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The American Heart Journal

VOL. 14 SEPTEMBER, 1937 No. 3

Original Communications

TREPOPNEA AS AN ETIOLOGICAL FACTOR IN PAROXYSMAL NOCTURNAL DYSPNEA*

FRANCIS CLARK WOOD, M.D., CHARLES C. WOLFERTH, M.D., AND ALEXANDER W. TERRELL, M.D.

PHILADELPHIA, PA.

IN A recent publication[1] attention was called to the fact that certain cardiac patients are comfortable in one recumbent position and uncomfortable in another.† This is probably due to movement of the heart in the chest under the influence of gravity. Individuals with this syndrome (trepopnea) usually prefer lying on the right side, and dislike lying on the left, but there are many variations. Persons with well-developed trepopnea are forced to abandon one recumbent position for another by intolerable symptoms, chiefly dyspnea, precordial pain, and cough. Our observations led us to suggest that, in some cases, trepopnea might play a part in the etiology of paroxysmal nocturnal dyspnea; that an attack of dyspnea might occur if a patient, while asleep, rolled into an unfavorable recumbent position. The present paper is a report of further evidence upon this question.

CASE 1.—J. D., a man of thirty-five years, had advanced rheumatic heart disease, mitral stenosis and insufficiency, marked cardiac enlargement, auricular fibrillation,

*From The Robinette Foundation, Medical Clinic, Hospital of the University of Pennsylvania.

†Since the publication of the paper on trepopnea, certain other pertinent references have been found.[2] Nélaton's paper[2a] is the earliest we have seen. He states that "some people cannot sleep on the left side, or if they can, their sleep is troubled and they do not get as rested as they do when they sleep in a favorable position." He mentions two earlier papers, by Arbey and by Piorry, to which we have not had access. Traube[2c] discusses the way in which a sick person learns to assume his most comfortable position. He uses the term "pseudo-orthopnoe" to describe the condition of a patient who assumes the upright position because of pain or cough, not because of dyspnea. (Possibly "pseudo-trepopnea" might be used in a similar way.) Von Dusch[2d] refers to a patient whose anginal attacks were precipitated by lying on the left side. Ebstein[2e] gives a very comprehensive review of all the various position preferences which sick individuals have. He has assembled a voluminous bibliography which we have used freely.

The rest[2g to 2p] are concerned mainly with measuring the degree of cardiac mobility, and with the question of whether the "Cor mobile," "bewegliche herz" or "wanderherz" produces symptoms. Determann[2o] reports the case of a patient with mitral stenosis who could not tolerate lying on the left side. He recognizes clearly that, when certain patients with heart disease lie on the left side, they are apt to have more marked distress than patients with mobile hearts without heart disease.

and definite trepopnea (R P L S).* When supine he experienced dyspnea and discomfort in the chest which forced him to turn. He had had attacks of nocturnal dyspnea since 1933. These paroxysms were his chief complaint. They were severe, lasting thirty to forty-five minutes, compelling him to get out of bed and lean forward. He stated that he had never awakened in an attack without finding himself in the supine position, and that he did not recall awakening on his back without being in the midst of a paroxysm. His wife volunteered the information that she had often seen him asleep on his back "panting" heavily. She had found that if she could roll him over on the right side, the "panting" would stop, whether or not she awakened him in so doing. If she did not turn him on his side, he would, before long, have one of his severe "spells."

CASE 2.—M. H., a woman of thirty-four years, had rheumatic heart disease, mitral insufficiency and stenosis, possible pulmonic insufficiency, moderate cardiac enlargement, left bundle-branch conduction defect, and trepopnea of choice† (R P S L). If she lay on the left side, she experienced shortness of breath, a choking sensation under the sternum, a pressing feeling over the heart, and a sense of fatigue. When first seen on March 2, 1936, the patient stated that she could not rest on the left side; if she turned on that side while asleep, she would wake up at once. We asked her to observe her symptoms and report to us later. When she returned she told us that on March 2 she had gone to sleep lying on the left side, despite moderate discomfort. During the night her husband found her asleep on her left side in a severe fit of "choking." He wakened her and helped her to sit up. She felt "smothered," "very tired," and "dizzy." She did not know what was wrong, but thought she was "ready to pass out." After some minutes she recovered. The patient was seen again on March 8, 1937, complaining of increased dyspnea and fatigue of a month's duration. She stated that occasionally during the past year, and three times during the preceding two weeks, her husband had found her lying on her left side, asleep, in the midst of a "choking attack," and had wakened her. She never experienced these attacks in any but the left lateral position. She obtained relief each time by rolling to the right side. Her sensations, on awaking, were a smothering, choking feeling, marked fatigue, and a "funny, sharp little pain" in the lower sternal region. On April 5, 1937, she came in again, with the report that on April 2 her husband had been wakened from sleep by strangling noises coming from her. He found her lying on the left side, in another severe choking fit. He awakened her, and helped her into a sitting position. She had marked dyspnea and cough for ten minutes, and was drenched with perspiration. After the attack subsided, she lay down on the right side and went to sleep, but even the next morning she did not feel quite like herself. The husband had never found her asleep on her left side, except when she was having an attack. For several days prior to this recent paroxysm of nocturnal dyspnea, she had been exerting herself more than usual helping a woman "clean house."

CASE 3.—R. M., a woman of forty-four years, had hypertensive cardiovascular disease and moderate enlargement of the heart, and suffered with both dyspnea and angina of effort. When we saw her on Nov. 12, 1936, she had trepopnea of necessity (R P S L). If she lay on the left side, she felt a pressing at the apex, extending to the left chest posteriorly (not anginal) and "got all stuffed up and couldn't breathe." She stated that often in the middle of the night, she had wakened lying on the left side, with a "funny, short cough," "all choked up."

*For the sake of brevity, an individual's relative preference for various recumbent positions will be indicated by a series of letters: R-right lateral; L-left lateral; P-prone; and S-supine. The first letter in the series is the most favorable position, the last letter is the most unfavorable. "R P L S" indicates that the patient is most comfortable on the right, least comfortable supine, and has an intermediate preference for the other two positions.

†"Trepopnea of choice" and "trepopnea of necessity" are used in this paper in the same sense that "orthopnea of choice" and "orthopnea of necessity" have been used in the past.

When symptoms were mild, she was able to terminate them by turning on her right side. When they were severe, she had to sit up for about five minutes before she could get her breath. She died of cerebral hemorrhage on Dec. 8, 1936. Necropsy disclosed a heart weighing 430 grams, with a thick left ventricular wall and sclerosed coronary arteries.

CASE 4.—G. H., a man of forty-three years, had rheumatic heart disease, moderate cardiac enlargement, mitral stenosis and insufficiency, and auricular fibrillation. Trepopnea (R P S L) was first noted in 1934, during an upper respiratory infection. Since that time it had fluctuated in intensity with variations in his circulatory efficiency. If he lay on the left side he experienced a "blowing up" in his left chest, shoulders, and arms, and felt choked. Sometimes a coughing spell occurred. When his trepopnea was marked, he frequently woke up on his left side in the middle of the night in an attack of dyspnea and cough, and had to sit up for many minutes to get his breath. He was convinced that these paroxysms were produced by turning on the left side during sleep. For some time he had tried to prevent this occurrence by putting a pillow close to his back as he lay on the right side so that he would have to "roll up hill" to get on the left side.

CASE 5.—M. C., a man of forty-two years, had syphilitic aortic insufficiency, marked cardiac enlargement, and congestion of the lungs. Trepopnea (P L R S) first appeared with the onset of congestive failure in January, 1936. The symptoms induced by lying on his back were dyspnea, choking, and discomfort in the center of the chest. In January, 1936, he began having the experience of waking up in the middle of the night, feeling short of breath and tired, as though he "had been running." He stated that he was usually lying on his back at such times. On further questioning he was not absolutely certain of this, but stated that the attacks must have been caused by lying on his back, because the sensations with which he awoke were identical with those he experienced during the day when he lay on his back for any length of time. On June 13, 1936, he entered the hospital with engorgement of the veins and liver, with no pulmonary congestion. Trepopnea and paroxysmal nocturnal dyspnea had both disappeared, but he preferred sitting to lying. He died of lobar pneumonia on Oct. 2, 1936. The heart weighed 900 grams and showed syphilitic aortic insufficiency.

CASE 6.—N. M., a woman of forty-three years, had congestive heart failure, syphilitic aortic insufficiency, large uterine fibroids, and a combination of trepopnea with orthopnea (R P S L). On Jan. 21, 1936, she was asked to lie on her left side. Within a minute she was forced to sit up, coughing and breathing heavily. The attack lasted five minutes. She stated that she often had attacks of this sort at night, which awakened her from sleep, but that when she awoke she was on her back, as a rule, not her left side. She died on March 7, 1936. The heart weighed 550 grams and showed syphilitic aortic insufficiency.

CASE 7.—W. S., a boy of seventeen years, had congestive heart failure, rheumatic mitral and aortic valvular disease, marked cardiac enlargement, and trepopnea of necessity (R S P L). When on the left side, he became cyanosed, the respiratory rate increased and he complained of pain in the right upper quadrant and a sense of choking. He stated that he had never experienced nocturnal dyspnea because he never had lain on the left side, even during sleep. On the night of March 17, 1937, the patient was asleep, lying on the right side. One of us turned him on the left side without waking him. He stayed in that position for twenty seconds. Then, without waking, he returned to the right lateral position. A second time he was turned on the left side. After fifteen seconds, he turned on the right, still asleep. A third time he was turned on the left side. This time he stayed there for a minute.

He then became quite dyspneic, woke up, sat bolt upright, almost before he was completely awake, breathed hard for half a minute, lay down on his back and went to sleep. The next morning, he had no recollection of these events. From March 17 to March 30, 1937, observation by the ward nurse demonstrated the fact that he never slept on his left side. On the latter date we again turned him into that position while he was asleep. He lay there for about half a minute. Then he began to cough and to breathe more forcefully. Shortly thereafter he awoke, and sat up coughing and breathing heavily for five minutes. After the cough subsided and breathing became normal, he lay down on his back and went to sleep. This paroxysm was like the one of March 17 except that it was of longer duration, cough was a prominent feature, and he remembered the episode the next morning. During the first week of April congestive failure began to subside. At the same time trepopnea diminished markedly. At a later date (April 24, 1937) the patient was able to sleep on his left side in apparent comfort.

The evidence supplied by the foregoing case reports would seem to warrant the following statements: (1) The manifestations of paroxysmal nocturnal dyspnea closely resemble certain of the symptoms of trepopnea: they seem identical to an observer, and to some patients who have experienced both. (2) Certain individuals with trepopnea, who have paroxysmal nocturnal dyspnea, believe that their nocturnal attacks are caused by the involuntary assumption of an unfavorable recumbent position during sleep. This belief is based upon their finding themselves in an unfavorable recumbent position whenever they awake in a paroxysm, and upon their being able to terminate mild attacks by turning over. The belief is so firmly fixed in some, that it has led them to adopt preventive measures (Case 4). (3) The wife in Case 1, and the husband in Case 2, felt convinced that the paroxysms of nocturnal dyspnea of their respective partners were produced by the assumption of one recumbent position, and were prevented or aborted by the assumption of another. (4) One man (Case 7) awoke with a paroxysm of nocturnal dyspnea when he was turned on the left side during sleep.

Consequently, it would seem that in some individuals, trepopnea is an etiological factor in paroxysmal nocturnal dyspnea.

These are selected cases, however, which illustrate only one aspect of the problem. Trepopnea and paroxysmal nocturnal dyspnea are not always associated in such an obvious etiological relationship.

(1) *There are patients with paroxysmal nocturnal dyspnea who do not have definitely demonstrable trepopnea.*—We have studied four such individuals. Two said that their attacks occurred only when they lay on the left side (Cases 8 and 9). Two others stated that they had no set position in which they awakened in attacks. (Cases 10 and 11.)

(2) *There are patients with paroxysmal nocturnal dyspnea and trepopnea who do not recognize an etiological relationship between the assumption of their unfavorable recumbent position and their nocturnal attacks.*—One patient had no knowledge of awakening with his attacks

in any constant position (Case 12). One believed that her position on awakening was not always an unfavorable one (Case 13). Three were convinced that their positions on awakening were often favorable ones (Cases 14, 15, and 16). It is true that individuals do not always know what they do at night (Case 7). Some of these patients may not really know in what position they awake. Moreover, they may produce their attacks by lying in their unfavorable position and may turn to a favorable one just before waking. Nevertheless, one should give as much attention to their negative testimony as to the positive statements of Cases 3 to 6, until one has the opportunity of testing their accuracy by watching them at night.

(3) *There are many patients with trepopnea who do not have attacks of nocturnal dyspnea.*—When this fact first came to light, it seemed difficult to understand. Most people are said to change position frequently during sleep. Therefore, it seemed reasonable to expect a trepopneic patient to get into his unfavorable recumbent position at some time during the night, and to be wakened by the ensuing symptoms. Study of the problem has shown that this is exactly what does occur. Most patients with trepopnea do awake at night with discomfort, which they believe to be caused by lying in an unfavorable position. However, dyspnea may be mild or absent. They may complain of (a) pain, anginal (Case 17), nonanginal (Cases 18, 19, 20, 21, and 22); (b) a combination of pain and dyspnea (Cases 23, 24, and 25); (c) palpitation (Case 26); (d) cough (Case 27); (e) indefinite sensations, probably a combination of dyspnea, palpitation, and discomfort (Cases 28, 29, and 30); (f) bad dreams (Case 31). Many of these symptoms have been mentioned by Weiss and Robb[3] as "equivalent manifestations of mild cardiac asthma."

There are a few patients with trepopnea who do not awake at night with the symptoms of this syndrome. First, there are individuals with mild degrees of trepopnea who can sleep in their most unfavorable recumbent position[1] (Cases 15 and 16). Second, there are persons who seem to be able to avoid their unfavorable position subconsciously without waking. One of our patients (Case 32) could probably do this; another (Case 7) certainly could.

Finally, it should be mentioned that there are persons with two unfavorable recumbent positions whose statements suggest that they avoid the worse subconsciously and awaken with cardiac symptoms in the better of the two (Cases 6 and 19).

(4) It has been reported that nocturnal dyspnea is common in aortic disease and hypertension, whereas it is uncommon in mitral stenosis and auricular fibrillation.[3, 5] This has not been found true of trepopnea. It is our impression that cases of these different types are wak-

ened with equal frequency by cardiac symptoms, but that patients with mitral stenosis and auricular fibrillation are less likely to have dyspnea as their primary symptom, and are more prone to experience palpitation and precordial discomfort; if attacks of dyspnea occur, they are apt to be of brief duration. The statement is also probably justified that dyspnea, as the primary cardiac awakening symptom, is less likely to be found in the patient with extreme congestive failure and severe trepopnea, than in the individual with cardiac insufficiency of lesser degree. It seems that a patient must be able to endure sleeping in his most unfavorable position for a considerable period, in order to bring on a severe, prolonged paroxysm of dyspnea. This does not appear to be possible for the most markedly trepopneic individuals.

The writings of Weiss and Robb,[3] Harrison,[4] and White and his coworkers[5] have included practically all available knowledge concerning the etiology of paroxysmal nocturnal dyspnea. It is probably the general impression that this knowledge is incomplete: that, in most instances, an adequate exciting cause for the attack has not been evident. Consequently, on the basis of the additional evidence contained in this paper, it might be worth while to review the subject.

It would appear that practically all cases of paroxysmal nocturnal dyspnea have a *predisposing factor*—something which produces an actual or latent failure of proper blood flow from the lungs to the aorta. This may be (a) left ventricular failure, (b) mitral valve obstruction, or (c) any other condition which might interfere with egress of blood from the lungs. In addition to this, a *precipitating factor* seems to be necessary—anything which can produce a sudden intensification of this failure of proper blood flow from the lungs to the aorta. This may be (a) the assumption of an unfavorable recumbent position during sleep (orthopnea or trepopnea), (b) a dream which gives rise to emotional disturbance or to physical effort, or in occasional cases[3] the onset of a paroxysm of arrhythmia or of a coronary occlusion. Conditions which may exaggerate the predisposing factor from time to time or facilitate the operation of a precipitating factor are hot weather,[4] abdominal distention[4] (stomach, bowels, or bladder), respiratory infection, and undue physical or emotional activity during the day. Furthermore, a low serum protein or an allergic tendency may increase the respiratory distress of an attack by superimposing upon it pulmonary edema and bronchospasm.

The recognition of trepopnea as a precipitating factor* supplies an explanation for the onset of attacks in many instances, which in the

*That others have been interested in a similar line of thought is shown by the following: Harrison,[4] in discussing the causes of paroxysmal nocturnal dyspnea, mentions the position of the body as an important factor. After describing the effect of orthopnea he states "some persons are likely to be short of breath when lying on the back, and some when lying on the left side." Weiss and Robb[3] recorded the fact that change from the supine to the prone position resulted in cessation of an attack, and that bending the head forward exerted a favorable effect.

past have appeared to have no adequate cause. Perhaps this concept will fill the most important gap in our knowledge of the etiology of paroxysmal nocturnal dyspnea.

If it can be demonstrated that an individual is likely to have an attack of paroxysmal dyspnea when he assumes a certain recumbent position during sleep, an attempt should be made to prevent him from doing so. One method is to fit him with a fairly snug woolen undershirt, with large wooden spools sewed to those sides which the patient should avoid.

Two other points concerning trepopnea might be mentioned: 1. Determann[2-6] made the observation in eight noncardiac patients that, immediately post partum, cardiac mobility increased tremendously. He described a patient whose apex impulse moved 1.5 cm. to the left before delivery. Shortly after delivery, the apex moved 9 cm. to the left, when the patient lay on the left side. The impulse was found, only after prolonged search, high in the axilla. He stated that this increased mobility lasted for several days; longer in multiparas than in primiparas. If his observations are accurate, trepopnea may be a factor in post-partum death in patients with heart disease. We have not as yet had the opportunity of studying this possibility. However, it seems to us suggestive that acute fatal cardiac failure tends to occur some hours after delivery when the patient is resting, rather than during delivery when the patient is subject to physical strain.

2. In our former paper[1] the statement was made that "it might be well, in nursing a cardiac patient, especially if he is narcotized or unconscious, for any reason, to be cognizant of the existence of this phenomenon" (i.e., trepopnea). "The order to turn the patient from side to side every hour may have to be modified." Case 33 demonstrates that this statement was justified. The patient had been trepopneic for some time but had been able to avoid lying on the left side until a cerebral embolus rendered her partly paralyzed and semistuporous. After that the order "turn the patient from side to side each hour" resulted in three serious circulatory attacks. When the etiological relationship of trepopnea to these attacks was recognized, the patient was kept off her left side and had no more such seizures. One of the standard textbooks on internal medicine, in discussing the treatment of hemiplegia, states that "owing to the frequency with which hypostatic pneumonia develops, the patient should be kept off his back and on the paralyzed side as much as possible." In certain patients with trepopnea, an alarming effect may be produced if this recommendation is carried out.

SUMMARY

Trepopnea is an etiological factor in the production of paroxysmal nocturnal dyspnea. In certain patients the relationship is definite. In others, however, the two syndromes are not obviously related.

Many persons with trepopnea do not experience paroxysms of nocturnal dyspnea. Some are wakened, when they assume an unfavorable recumbent position during sleep, by symptoms other than dyspnea: especially pain, palpitation, and cough. Some are able to avoid their unfavorable recumbent positions subconsciously, without waking. If a trepopneic individual becomes unconscious or paralyzed, the responsibility for avoiding an unfavorable position may devolve upon the physician and nurse.

Patients with mild degrees of trepopnea usually are capable of sleeping in their most unfavorable recumbent positions. However, if further impairment of blood flow from the lungs to the aorta occurs, either temporary or permanent, the assumption of an unfavorable position during sleep may initiate a severe attack.

The demonstration that trepopnea is a precipitating factor in paroxysmal nocturnal dyspnea supplies an explanation for the onset of attacks in certain cases where formerly no adequate cause was recognized.

CASE REPORTS

CASE 8.—On Nov. 16, 1935 a physician (D. T.), fifty-two years of age, consulted us. On three different occasions during the preceding three months he had awakened from a sound sleep with dyspnea so urgent that it had forced him to sit up. Each time he had awakened he had found himself lying on the left side. He volunteered this information without knowledge of our interest in trepopnea. Careful examination of his cardiovascular system elicited no evidence of disease. (This patient was mentioned in a previous paper.)[1]

CASE 9.—Z. W. was seen in the cardiac clinic on March 12, 1936. He was a short, heavy-set negro laborer of forty-five years, with diabetes, a negative Wassermann reaction, dyspnea on climbing stairs, and no definite objective evidence of cardiovascular disease. The tentative diagnosis was coronary artery disease. Trepopnea was not clearly demonstrable. All recumbent positions could be tolerated, but in certain of them symptoms were experienced: The right lateral position made him feel as if his breath did not "go all the way down"; the prone position caused him to be "tired around the heart"; in the left lateral position he felt a "heaviness over the heart," and "every now and then my breath gets a little short"; the supine position was comfortable, if he used two pillows. For a year he had noticed that if he went to sleep on his left side, he would wake up "seared, fightin', and hollerin'." He would think he was in a whirlwind, in a storm, or in the water drowning and trying to escape. When he awoke his heart thumped so hard that he often asked his wife if she could hear it (which she could not). He was badly "choked up" and so short of breath that he had to sit up for three to five minutes. Almost all of these attacks arose when he was on the left side, asleep. He experienced them very occasionally if he lay on his back with his head too low. Both he and his wife stoutly maintained that the "witch-ridin' spells" never occurred in any other recumbent position. These attacks constituted his chief complaint. (This patient was mentioned in a previous paper.)[1]

CASE 10.—A. F. was a forty-one-year-old Italian tailor with extreme hypertension (210/150), slight cardiac enlargement, and slight edema of the feet, who was seen

in the cardiac clinic on Oct. 26, 1936. He had experienced four attacks of nocturnal dyspnea during the preceding two weeks. All but the last had been severe. For years he had slept on his right side by preference. Sometimes he slept on the left side. He said he "no can catch sleep" when he lay on his back, but trepopnea could not be demonstrated. He did not recall awakening in any particular recumbent position when he had his attacks.

CASE 11.—J. S., a forty-nine-year-old Italian man, had degenerative cardiovascular disease and moderate cardiac enlargement. Although he was more comfortable on the right side and back than on the left, trepopnea could not be demonstrated. He had paroxysms of nocturnal dyspnea, which did not seem to him to be related to any particular recumbent position. There was a question of a possible allergic factor, since the attacks were relieved by epinephrine.

CASE 12.—A. H., a colored truck driver, thirty-six years old, had mitral stenosis, auricular fibrillation, marked cardiac enlargement, and trepopnea of necessity (R P S L). Smothering and a sense of fatigue became intolerable if he lay on the left side. About a dozen times during 1936 and the spring of 1937, he had awakened at night "all smothered," without cough, feeling that there "was not enough air in the room," and that he could not get his breath. (He made a motion suggesting that there was a bag covering his head.) At such times he would sit up, get no relief; then get up, "stir around," and go nearer the window. It took about half an hour for the attack to pass off. He did not remember in what position he awoke. However, he said that the sensation with which he awoke was exactly like that caused by lying on the left side, only "much worse."

CASE 13.—L. A., a woman of twenty-nine years, had mitral insufficiency and stenosis, possible pulmonic insufficiency, marked cardiac enlargement and trepopnea of choice (R S P L). On Oct. 6, 1936, she awakened in the middle of the night, lying on the left side, with shortness of breath, and a "short, funny, cough." She rolled to her right side and obtained relief in a few minutes. During the next week, she experienced several similar nocturnal attacks. When questioned on October 12 she stated that almost always when she awoke in an attack she was on her left side. Once or twice she thought she was lying on her back.

CASE 14.—G. C., a man of fifty-seven years, had hypertensive cardiovascular disease, syphilis, slight aortic insufficiency, considerable cardiac enlargement, and trepopnea of necessity (R P S L). He was watched at night by the ward nurse, and was never seen sleeping on the left side. There was a definite history of paroxysmal nocturnal dyspnea, but no attacks were observed while he was in the hospital. He did not believe that he awoke on the left side in attacks, but rather on the right. We attempted to turn him on his left side while he slept, but never succeeded in doing so without awakening him.

CASE 15.—J. R., a forty-eight-year-old Italian man, had hypertensive cardiovascular disease, marked cardiac enlargement, left bundle-branch block, and trepopnea of choice (R P S L). He often awoke with nocturnal dyspnea, but believed that he was in the right supine position (a position which he liked) at such times, not on the left. He said that if he rolled on the left side during sleep, he would wake up with a start, and would have to sit up for a while to get his heart quieted down. However, the ward nurse reported that he often slept on the left side.

CASE 16.—I. P., a man of fifty-one years, had marked cardiac enlargement and congestive heart failure, probably due to coronary artery disease. He had trepopnea of choice (R S P L). He stated that he had often awakened at night in a paroxysm of

dyspnea, but did not believe he had been lying on the left side at such times. The ward nurses reported that he often slept on the left side at night. He was never observed in an attack of nocturnal dyspnea.

CASE 17.—M. G., a colored woman of sixty-seven years, had hypertension, angina pectoris, and moderate cardiac enlargement. She preferred to lie prone or on her right side. If she turned on her back during sleep, or if she slipped down off her two pillows, she would awaken with severe upper sternal pain exactly like that which she experienced on effort.

CASE 18.—J. G., a colored man of fifty-one years, had hypertension, marked cardiac enlargement, and trepopnea of necessity (R P S L). He often woke up at night when he rolled on the left side. The sensation which would waken him was a severe pain over the precordium. It was usually relieved when he turned on the right side. Sometimes it did not disappear until he sat up. The pain was accompanied by a slight choking feeling, but not by real shortness of breath.

CASE 19.—E. W., a woman of twenty-two years, had rheumatic heart disease, mitral insufficiency and stenosis, moderate enlargement of the heart and trepopnea of necessity (P R S L). For a long time she had been wakened about once each night by sharp pain through her left chest, throbbing of the heart, and a moderate sense of choking. At such times she found herself on her back. She could roll over on her face and obtain relief in about five minutes. She had never awakened lying on the left side.

CASE 20.—C. C. was a very large Italian woman, 5 feet in height, who weighed over 300 pounds. She had hypertension, nephritis, moderate cardiac enlargement, and trepopnea of necessity (R P S L). She stated that once every week or two she would wake up at night lying on the left side with a severe pain over her heart, and a marked feeling of fatigue. These symptoms were of such degree that she was powerless to turn by herself. She had to wake her husband, who rolled her on her right side. She then obtained relief. Shortness of breath was not present during these episodes.

CASE 21.—V. R., a man of forty-four years, had rheumatic heart disease, mitral insufficiency and stenosis, auricular fibrillation, marked cardiac enlargement, and trepopnea of necessity (P R S L). He said that once in a long while he rolled on the left side during sleep. Whenever this happened he would wake with pain in the precordium, in the left shoulder, and in the right hypochondrium. Shortness of breath was not a definite feature.

CASE 22.—A. V., a man of fifty-nine years, had rheumatic heart disease, moderate cardiac enlargement, mitral stenosis, auricular fibrillation, and trepopnea of necessity (R P S L). The first three positions were all comfortable. The left lateral position caused precordial pain. He often awoke at night lying on the left side, with a severe "bruised feeling" over his heart. He turned to the right and it disappeared.

CASE 23.—H. B., a man of twenty-four years, had rheumatic heart disease, mitral and aortic valvular lesions, extreme cardiac enlargement, auricular fibrillation, and trepopnea of necessity (L P R S). He stated that he was frequently awakened in the middle of the night, lying on his back or on his right side, by "feeling a heavy weight" on his chest. He was usually a little dyspneic at such times, and might have a brief coughing spell, but as a rule shortness of breath and cough were not the outstanding symptoms.

CASE 24.—L. F., a woman of forty-eight years, had advanced rheumatic heart disease, marked cardiac enlargement, mitral insufficiency and stenosis, auricular fibrillation, and trepopnea of necessity (R S P L). She told us that she often awoke at night, lying on the left side, with pain over her heart, a peculiar heavy feeling in the whole left side of the chest, marked fatigue, and a sense of choking. Dyspnea was secondary, cough was absent. She sat up for a few minutes, then lay down on the right side and went to sleep.

CASE 25.—E. M., a woman of fifty-nine years, had hypertension, severe angina of effort, marked cardiac enlargement, and trepopnea of choice (L R P S). She often awoke at night with a choking sensation, found herself on her back, rolled to one side or the other, and experienced relief. She stated that this sense of choking was a combination of "pressure and smothering."

CASE 26.—M. R. was a colored woman of fifty-five years, who had syphilis, hypertension, moderate cardiac enlargement, and trepopnea of choice (R S P L). She told us, "If I turns on my lef' at night, I wakes right up. I has a scary feelin', and my heart is goin' hard or goin' wrong or somethin'." She also described a pressure over her heart. She did not experience real dyspnea or pain.

CASE 27.—J. F., a man of fifty-five years, had coronary artery disease, angina of effort, and slight cardiac enlargement. Lying on the left side made him cough. He stated that he often rolled on the left side while asleep, but whenever he did, he awoke promptly. He would sit up, belch twice, cough a few times, then lie down on his right side and go to sleep again. Long before we first saw him he made a study of his trepopnea. On several occasions he lay on the left side as long as he could. Coughing spells lasting a minute or two resulted, but he never had a real paroxysm of dyspnea. He believed that the cough saved him from having a bad spell at night, because it wakened him before he got in bad condition. The sensation that caused him to cough was a tickling in the pharynx, not down in the chest.

CASE 28.—C. C., a woman of seventy-five years, had degenerative heart disease, moderate cardiac enlargement, auricular fibrillation, and trepopnea of necessity (R S P L). She had been tested repeatedly, and could never tolerate lying on the left side for much more than a minute. Usually she was forced to change her position in less than thirty seconds. The symptoms she described were a pain over the heart, and a choking, breathless feeling. She stated that she could never sleep on the left side. If she rolled on that side during sleep, she "woke up right away." She did not know what the sensations were which woke her.

CASE 29.—J. P. was a man of thirty-five years who was in the hospital in November, 1935, with congestive failure. He had rheumatic heart disease, mitral and aortic valvulitis, marked cardiac enlargement, and auricular fibrillation. When first admitted he had trepopnea of necessity (R P L S). If he lay on his back he experienced a smothering sensation and cough. He stated that if he turned on his back during sleep he would "wake up right away." He did not know what wakened him. The ward nurse watched him at night and never saw him lying on his back asleep until congestive failure cleared up, and trepopnea markedly diminished.

CASE 30.—R. O. was a woman of twenty-five years, who died in the hospital on Dec. 6, 1935, with congestive heart failure. She had rheumatic heart disease, mitral and aortic valvulitis, marked cardiac enlargement, auricular fibrillation, and trepopnea of necessity (R P S L). During waking hours she could not tolerate lying on the left side for more than half a minute because of shortness of breath, a "stuffy

feeling,'' and precordial oppression. She said that now and then she awakened at night with a peculiar feeling that ''something was wrong,'' found that she was on the left side, rolled to the right, and became comfortable at once.

CASE 31.—J. H., a colored man of fifty-nine years, had degenerative heart disease and trepopnea of choice (R S P L). He stated that whenever he turned on the left side at night he had awful dreams—that he was running or falling—which woke him up.

CASE 32.—W. A. was a man of twenty-six years who had congenital heart disease, and a rough systolic murmur and thrill at the base of the heart and along the midsternum. There was no cyanosis. The heart was slightly enlarged. Exercise tolerance was definitely reduced. Trepopnea of choice became trepopnea of necessity (P L R S) when he had a cold. He stated that he never got on his back when asleep. He never had found himself in that position on awakening. Moreover, he never had been awakened at night by dyspnea or by throbbing in the chest (the symptoms he experienced during waking hours if he lay supine).

CASE 33.—Mrs. W. W. A. was a patient of fifty-nine years, whose case had been reported to us by a fellow physician. She had rheumatic heart disease, mitral stenosis, auricular fibrillation, and marked enlargement of the heart. On Feb. 23, 1937, she suffered a left hemiplegia, presumably from a cerebral embolus, and became semi-stuporous. In an attempt to prevent hypostatic pneumonia, the nurses were ordered to turn the patient periodically from side to side.

On February 24 her physician received a telephone call to come at once, the patient was having a severe ''heart attack.'' She was reported to be lying on the left side. The order was given to turn her on her back and give her caffeine. By the time the physician arrived, she looked as well as before. This happened twice more, each time when the patient had been turned on the left side. The attacks were alarming. The pulse rose to 140, and became weak. Cyanosis became quite marked. The nurse believed the patient to be dying. After the third attack, she was studied from the standpoint of trepopnea: When turned slightly to the left, she was comfortable. When turned halfway to the left, after ten minutes she became cyanosed, the heart rate increased markedly, the pulse became weak, and the patient ''looked terrible,'' as though she were going to die. Cough was not present. No change was noted in the breathing. Shortly after she was turned off her left side, these alarming phenomena disappeared. When the nurses were asked if the patient ever had had attacks of this sort when not on the left side, they disagreed.

No history of paroxysmal nocturnal dyspnea could be obtained. Prior to the present illness, the patient had told her housekeeper that she did not like to lie on the left side because it made her feel dizzy and light-headed. Needless to say, she has been kept off her left side since the relation between trepopnea and her attacks was discovered.

One other fact came out in discussing the case with her physician: on a certain day, one of the patient's two physicians saw her, thought she was looking very well and gave a cheerful prognosis. Just as he left he asked the nurse to turn the patient on the left side. He felt that, in this position, she would be able to breathe more freely with her right (unparalyzed) side.[6] Ten minutes later, the other physician called, and thought that the patient was moribund.

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CLINICAL STUDY OF A PREPARATION OF SQUILL (URGININ) IN THE TREATMENT OF MYOCARDIAL INSUFFICIENCY*

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HISTORICAL NOTE

SQUILL is one of the oldest of medical remedies. Prepared from the bulb of the sea onion *(scilla maritima)*, it is said to have been introduced into practice by Epiminides or Pythagoras. The earliest reference to it is found in a medical prescription contained in the Ebers papyrus, about 1500 B.C. In Egypt, the plant was worshipped as a protector against evil, and temples are said to have been erected in its honor. Its consumption is mentioned by Galen, particularly as an aid to longevity. Hippocrates used it externally as an irritant; by others it was employed to promote perspiration and the flow of urine. Later, the external application was abandoned, although it continued in high favor as a diuretic, expectorant, and emetic. In a sixth century manuscript of Dioscurides appears an excellent drawing of the squill plant. Gradually, it fell into disuse, apparently because of its tendency to induce nausea and vomiting.[1, 2, 3]

In the middle of the eighteenth century (1746), van Swieten,[4] pupil of Boerhaave, rediscovered and stressed the efficacy of dried, powdered squill in the treatment of dropsy. The effects on the heart largely escaped notice although Francis Home,[5] Professor of Materia Medica in the University of Edinburgh, in 1780 advised large doses and noted that after a few days "nausea and vomiting came on" and the pulse was then "remarkably slow," sometimes 40. In 1784, the eminent Dr. Samuel Johnson was taking "vinegar of squills" with excellent effect, voiding as much as 20 pints in the course of a day.[6] Yet, when in the following year, Withering[7] published his monograph on the foxglove, the sea onion appears to have been largely forgotten and, for over a century and a half, digitalis has maintained, undisputed, its title as the sovereign remedy in the treatment of cardiac disorders.

The position of squill as a member of the digitalis group was recognized by Fagge and Stevenson[8] in 1865, on the basis of its action of the frog's heart, which they observed was similar to that of the foxglove. Dixon and Haynes[9] first prepared a tincture assayed on frogs,

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in 1906. But it remained for Mendel,[10] in 1918, to describe in detail pharmacological and clinical studies which aroused renewed interest in the drug and indicated its usefulness in cases of cardiac insufficiency. Added impetus was afforded by the work of Stoll[11] and his collaborators, who, in a series of researches extending from 1921 to 1935, isolated and established the chemical formula of the glucoside, scillaren. In 1934, methods were developed for extracting in pure form the two water-insoluble glucosides, scillonin A and B, which are contained in the preparation used in the present study.[12]

LITERATURE

The number of publications dealing with the clinical use and experimental study of squill is enormous. Many of the observations on patients are not pertinent to the present discussion because they are concerned with its action in noncardiac disorders. Its effectiveness in the cure of dropsy, due to its diuretic action, was known for centuries; but, as was at first the case with digitalis, no proper distinction was made between the accumulation of fluid in the tissues resulting from cardiac failure and edema developing from other causes. Later, when it was recognized that squill was primarily a cardiac remedy, belonging to the digitalis series with respect to its action on the heart, more accurate clinical observations were recorded. But the effects were variable and inconstant, largely because preparations were used having different content, potency, and absorbability. In 1922, Robinson[13] wrote: "squills, as well as most of the purer derivatives of digitalis, are so poorly absorbed from the gastrointestinal tract that they should never be used for oral administration." Sollmann,[14] in the 1936 edition of his *Manual of Pharmacology*, states that "the poor absorption renders it undesirable as a digitalis substitute."

During recent years, many attempts have been made to isolate various active principles, but most of those obtained have been only a little purer than the crude extracts. A number have been mixtures of several glucosides. Scillaren, previously mentioned, is said by Stoll[11] to have a "high therapeutic index" and to be rapidly eliminated. Numerous reports of its effects in patients have been made.

Thus far, two papers have been published concerning the clinical use of urginin. Carr and Mayer[15] made observations on 85 patients with cardiac decompensation. They concluded that this preparation (then known as scillonin), will produce the usual effects of digitalis. Cardiac irregularities are likely to be the first sign of dangerous intoxication. Nausea does occur and may precede the appearance of arrhythmias; it appears to signify a more advanced grade of intoxication than when due to digitalis. Slowing of cardiac rate to 60 or below is frequent. All of these effects call for temporary cessation of

therapy. A dose of from 8.0 to 12.0 mg., depending on the weight of the patient, may be given within four days to patients who have not taken a drug of the digitalis group within two weeks. The maintenance dose is approximately 0.5 mg. per day, but it may be as low as 0.33 mg. The use of urginin is of advantage in certain persons who take digitalis with difficulty because of gastric distress early in the course of medication.

A study of the effects of urginin on the electrocardiogram was reported by Maher and Sittler.[16] Twenty-five cases of heart disease, with edema, were studied in the Cook County Infirmary. The dosage ranged from 1.0 to 3.0 mg. daily, for varying periods. There was a wide variation in the degree of effect produced, implying either differences in absorption or in the response of the patient. In therapeutic doses, they observed, as with digitalis, changes in the R-T or S-T segments, slight prolongation of the P-R interval and occasional extrasystoles. The ventricular rate was decreased in 21 of 25 patients; the decrease occurred in the presence of sinus rhythm as well as in auricular fibrillation. The effects of over-dosage were the production of frequent extrasystoles, marked prolongation of the P-R interval and auricular fibrillation.

MATERIAL AND PROCEDURE

A clinical study was made of the effects of the preparation of squill, known under the trade name of urginin, on 62 patients in the wards of the hospital. Forty-three suffered from congestive heart failure; the cardiac disease was of varied etiology—rheumatic, syphilitic, arteriosclerotic, and hypertensive. The group of 19 without failure, similarly studied for comparison, comprised patients with affections of the heart as well as some ill of other disorders. A standard routine was followed and all observations were recorded graphically on individual charts. Patients were selected for study who had received no digitalis for at least fourteen days. Sedatives were given as indicated. Cascara and mineral oil were used as cathartics.

A control period of three days of rest in bed preceded administration of urginin, except in a few cases in which therapy seemed urgent. The diet was low in salt and bulk. The symptoms and signs of cardiac insufficiency, temperature, heart rate, and fluid intake and output, were noted daily. The patients were also weighed each day, if their condition was satisfactory. Observations of arterial blood pressure, venous pressure, circulation time, vital capacity, leucocyte count, and erythrocyte sedimentation rate were made at frequent intervals. Electrocardiograms were taken daily during the first ten days, and from two to five times weekly thereafter.

THE DRUG

Urginin* is derived from *Urginea maritima* and is a mixture, in approximately equal proportions, of 2 of the active, water-insoluble glucosides—crystalline scillonin A and amorphous scillonin B. The process for extracting these glucosides of squill was perfected by Dyas and Ingersoll.[12] Their chemical behavior is still imperfectly understood, so that biologic assay is necessary to insure uniform potency. For clinical use, urginin is put up in tablets containing 0.5 mg. of the mixed glucosides.

Biologic assay by the intravenous cat method has shown that 1 tablet (0.5 mg.) has an average potency of 2.13 cat units.[17] One cat unit contains approximately 0.202 mg.[18] The tablets are said to retain this potency unimpaired for at least one year.[15] In dogs, crystalline scillonin is less than half as cumulative as ouabain and less than one-third as cumulative as digitalis. The acute toxic effects of scillonin in the dog and cat (continuous intravenous infusion) are as great as those of ouabain. In the frog, they are less.[19] When the crystalline and amorphous scillonins are combined, as in urginin, these individual effects are probably modified.

EFFECTS IN PATIENTS

In the presence of cardiac insufficiency, the results were similar to those customarily obtained with digitalis.[15] The signs and symptoms of congestive failure tended to disappear. As a rule, edema, when present, was lost and diuresis occurred (Figs. 1 to 5). Occasionally, elimination of fluid was not complete and the administration of a mercurial diuretic (salyrgan or mercupurin) resulted in further augmentation of urinary output and continued loss of weight (Fig. 2). In cases of auricular fibrillation, the ventricular rate was slowed (Figs. 1, 2, 3 and 6). As is the case with digitalis, equally striking results were obtained in the presence of regular (sinus) rhythm (Figs. 4 and 5). When improvement occurred, the venous pressure fell, circulation time decreased and vital capacity increased. There was no specific effect on systolic or diastolic blood pressure. Such changes as occurred were apparently associated with alterations in the state of the heart and circulation; they could not be ascribed to the action of the drug.

In the presence of sinus rhythm, the rate was slowed at least 10 beats in about one-half the cases. The effect on rate cannot be ascribed directly to the action of the drug; the heart slows as the circulation improves, and particularly as diuresis occurs and venous pressure falls. In 22 of 24 cases of auricular fibrillation, the ventricu-

*Urginin is the trade name for a product marketed by the Calco Chemical Co., Inc. It was accepted, in 1934, by the Council on Pharmacy and Chemistry of the American Medical Association for inclusion in *New and Nonofficial Remedies*. See J. A. M. A. 103: 1708, 1934.

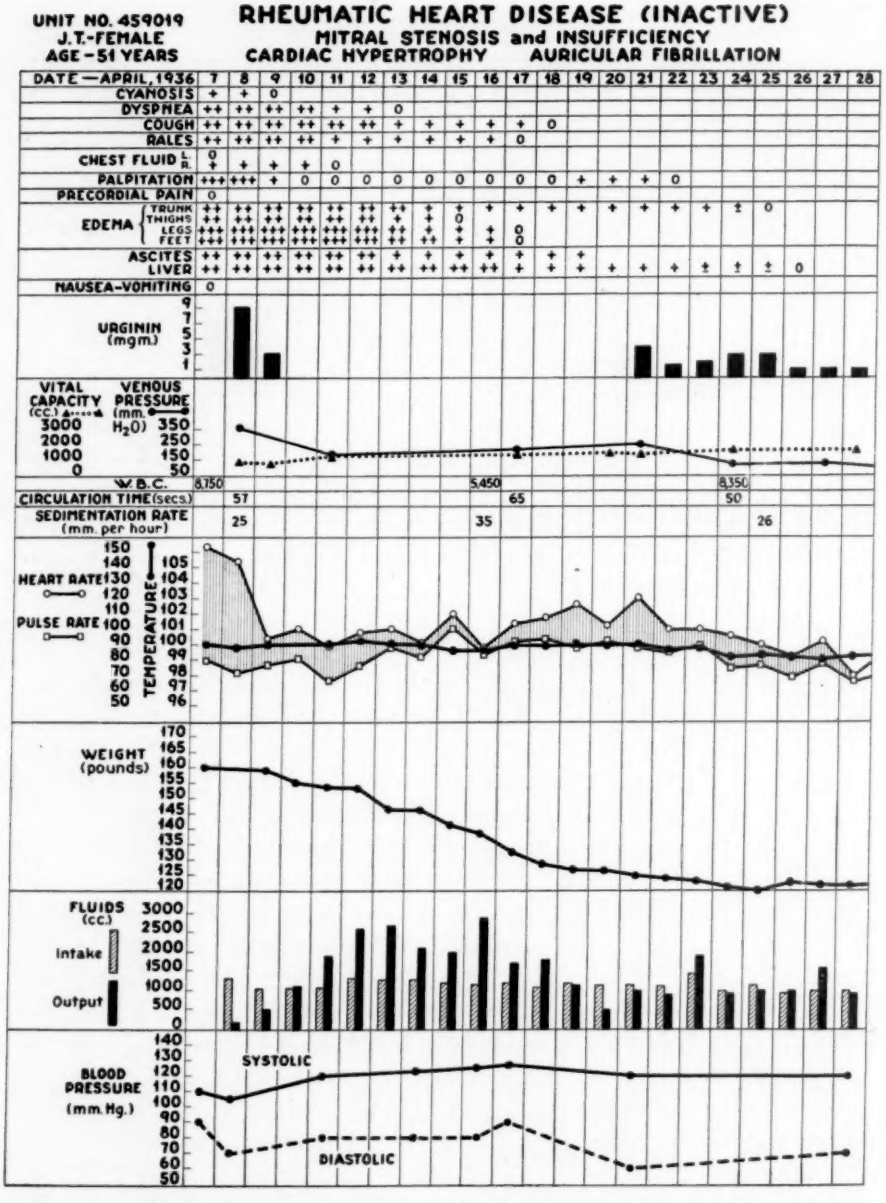

Fig. 1.—Advanced cardiac insufficiency in which the critical condition of the patient made prompt treatment imperative. Administration of 12.0 mg. of urginin in two days was followed by partial relief of symptoms, fall in venous pressure, increase in vital capacity, slowing of heart rate, progressive loss of weight, and marked diuresis. There was no significant change in arterial blood pressure. There were no toxic effects. After stopping urginin therapy, the heart rate became progressively more rapid beginning on the sixth day. The venous pressure rose and the urinary output diminished. Additional doses of urginin, smaller than those originally given, produced greater relief of symptoms and signs of cardiac insufficiency, with further fall in venous pressure and renewed diuresis.

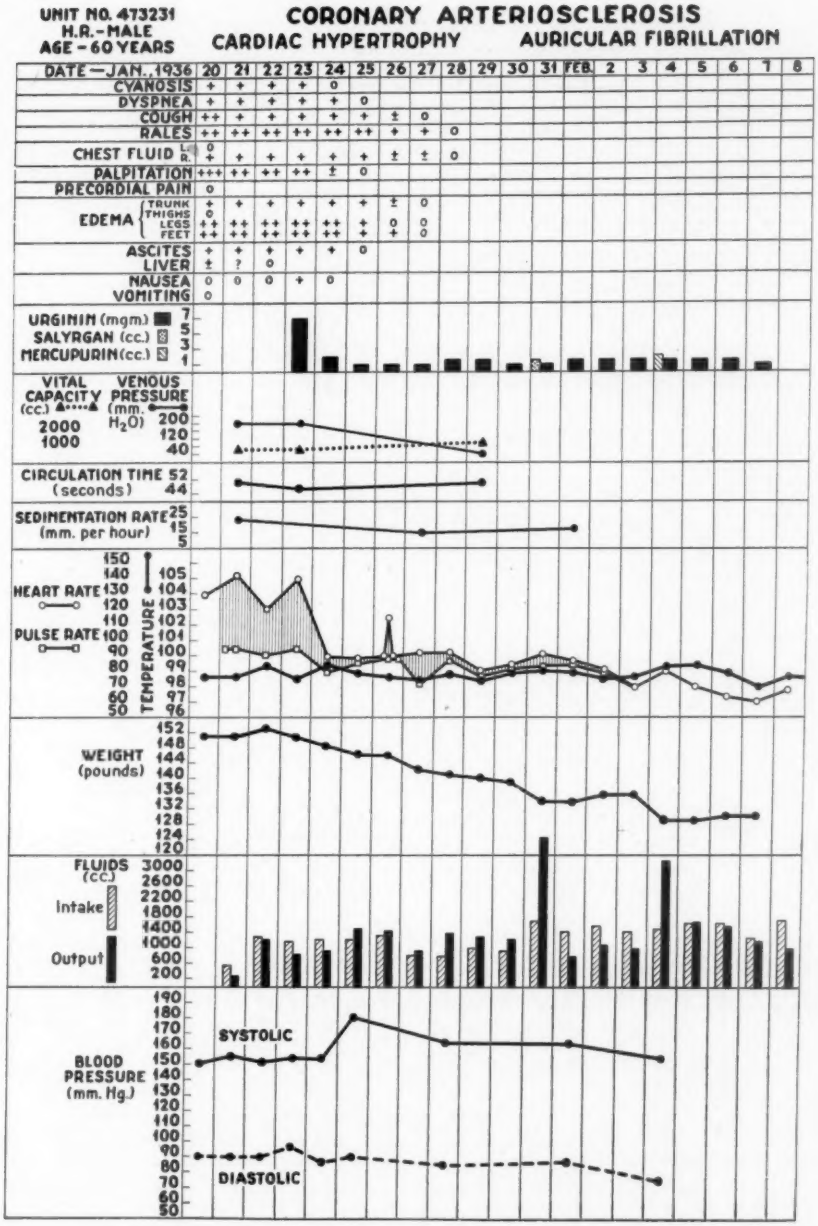

Fig. 2.—Moderately advanced cardiac insufficiency, in which there was no improvement during a control period of three days without medication. Urginin therapy was followed by disappearance of signs and symptoms. Venous pressure fell, vital capacity increased and there was a sharp decrease in heart rate. The weight diminished gradually concomitantly with moderate diuresis. As the circulation improved, the systolic blood pressure rose and the diastolic level was slightly lowered.

All of the retained fluid was not eliminated, however, as shown by tremendous urinary output on January 31, following intravenous injection of salyrgan. Marked diuresis and further loss of weight occurred four days later (February 4) after injection of mercupurin.

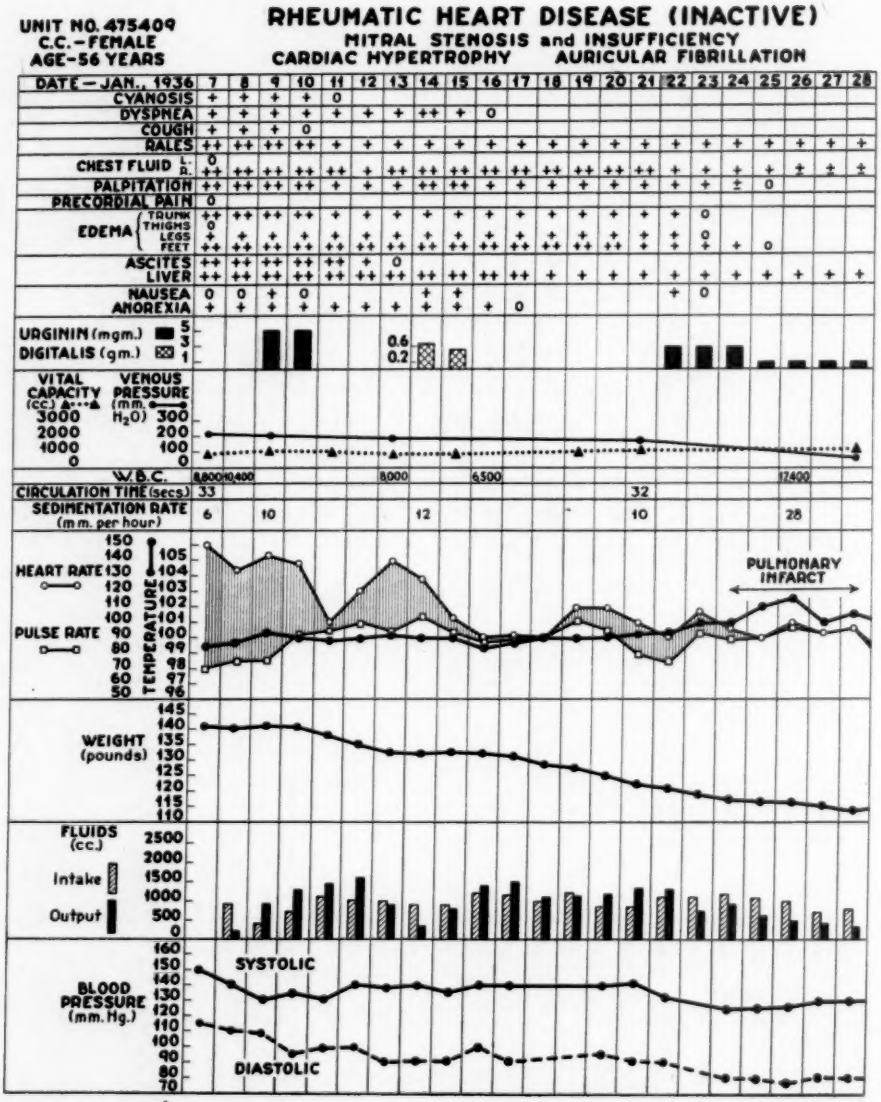

Fig. 3.—(See also Fig. 6.) Advanced cardiac insufficiency with auricular fibrillation and rapid ventricular rate. The heart rate fell from 160 to 100 after 10.0 mg. of urginin, given in two days. There was good diuresis and gradual loss of weight. Urginin was discontinued and after three days, the rate again rose to 140; diuresis and loss of weight ceased. Digitalis, 1.1 gm. of powdered leaf, given in two days, again slowed the rate and induced diuresis with an associated loss of weight. There was further improvement when urginin administration was resumed after an interval of seven days. Pulmonary infarction did not materially interrupt the otherwise favorable course of progress.

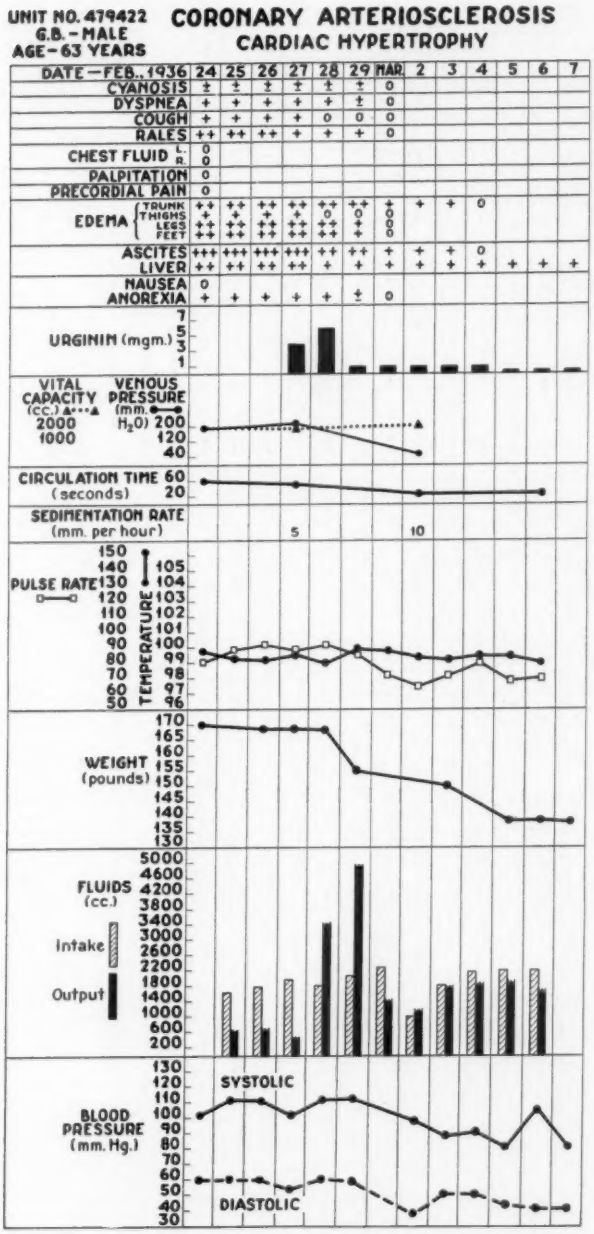

Fig. 4.—Advanced cardiac insufficiency in which there was no change in the picture during a control period of three days, during which no medication was given. Marked clinical improvement was induced by 10.0 mg. of urginin given in two days, followed by smaller maintenance doses. Venous pressure fell, vital capacity increased and circulation time became more rapid. The heart rate was slowed, although the rhythm was regular. There was tremendous diuresis and associated loss of weight. The level of arterial blood pressure, both systolic and diastolic, was lowered.

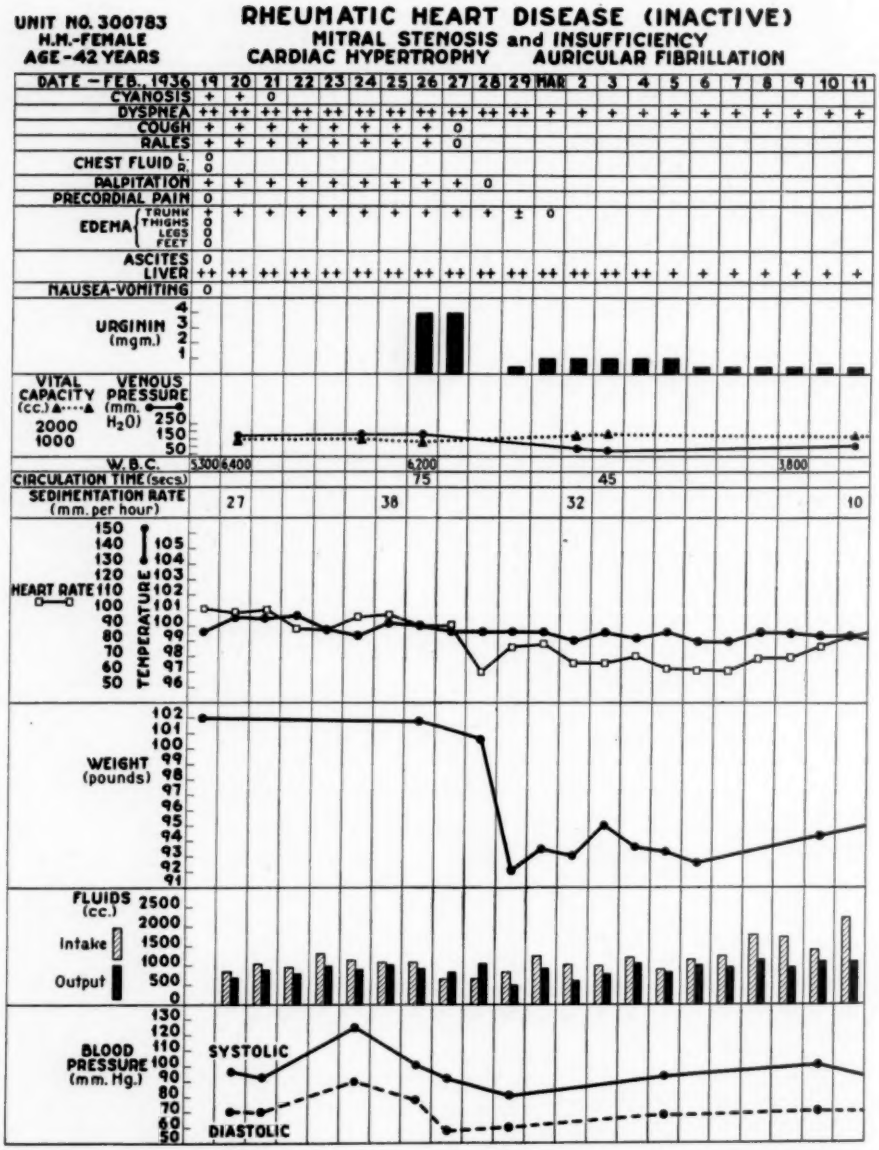

Fig. 5.—Moderately advanced cardiac insufficiency in which a control period of seven days rest in bed without medication was not followed by improvement. Although auricular fibrillation was present, the heart rate was not very rapid. Administration of 8.0 mg. of urginin in two days induced relief of symptoms and signs, slowed the ventricular rate, lowered venous pressure, increased vital capacity and accelerated circulation rate. There was marked and rapid loss of weight, unaccompanied by correspondingly large diuresis. It is probable that all of the urine was not collected and measured. Compensation was maintained by continued small doses of urginin.

lar rate fell from 10 to 70 beats per minute. In two patients with hyperthyroidism the drug did not appear to affect rate.

When edema was present, diuresis was the rule unless the patients were moribund or the heart was unresponsive to all therapeutic efforts. In patients without cardiac disease to whom the drug was given, no increase in urinary output occurred. Nine cases had persistent edema after partial improvement was brought about by urginin; all responded with large diuresis to intravenous injections of salyrgan or mercupurin. It appears that the two scillonins contained in urginin exert no specific stimulating effect on the kidneys. As is the case with digitalis, such diuresis as occurs in congestive heart failure is probably secondary to improvement in the renal circulation.

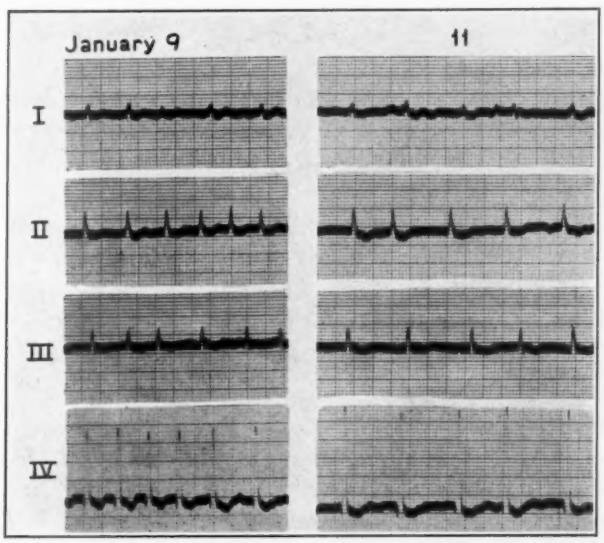

Fig. 6.—Slowing of ventricular rate and T-wave changes produced by urginin in a case of auricular fibrillation.

Unit No. 475409. Female, aged fifty-six years. Diagnosis: Arteriosclerosis; coronary sclerosis; cardiac hypertrophy; permanent auricular fibrillation; cardiac insufficiency (moderate).

January 9: Rate 160. After control record was taken, urginin 5.0 mg. was given. January 10: 5.0 mg. January 11: Rate 100; T_1 partly inverted; T_2 deeper.

One case of persistent auricular tachycardia, unresponsive to digitalis, did not show a change in rhythm after urginin.

Premature beats disappeared in 10 patients after treatment.

DOSAGE

The effective dose, that is, the amount necessary to bring about the optimal therapeutic result, was estimated on the basis of clinical observation and the effect on ventricular rate in cases of auricular fibrillation. In terms of cat units, it was a little more than twice that of digitalis. Thus, one tablet of urginin (0.5 mg. or 2.13 cat units) is not quite equivalent in therapeutic potency to one tablet of com-

mercial digitalis (0.1 gm.) when the latter is assayed to equal one cat unit. For clinical purposes, 0.5 mg. of urginin may be regarded as equal in therapeutic efficacy to 0.1 gm. of a preparation of digitalis standardized in this manner. In other words, approximately two cat units of urginin, orally administered, are required to induce the same effects as one cat unit of digitalis. This difference in the two drugs, between the potency established by biologic assay and that observed clinically, is due probably to less complete absorption or more rapid elimination in the case of urginin.

The *total effective dose* was calculated by subtracting from the full amount given, the quantity theoretically excreted each day. It ranged, in different patients, from 6.5 to 14.0 mg., with an average of 9.0 mg. (18 cat units). Similar variations in digitalis dosage are commonly seen, depending on the etiology of the cardiac lesion, the degree of cardiac insufficiency and on individual idiosyncrasy.

The *daily maintenance dose* was determined by observing the amount required to keep the ventricular rate at a given level in cases of auricular fibrillation; or, in the presence of sinus rhythm, to maintain changes in the form of the electrocardiogram after these had appeared. In cases of cardiac insufficiency with auricular fibrillation, it ranged from 0.5 to 2.0 mg., with an average of 1.05 mg. The average for cases with hyperthyroidism was 1.22 mg., while for those with normal metabolic rates it was 0.89 mg. In the cases with sinus rhythm, it ranged from 0.5 to 1.5 mg., with an average of 0.95 mg. The average daily maintenance dose for all cases, excluding those with hyperthyroidism, was 0.92 mg.

The effective dose was given over periods varying from one to six days. Large, single doses often caused nausea or indigestion; after this became apparent, they were avoided unless advanced congestive failure demanded rapid relief. A satisfactory scheme of dosage was to give 1.5 mg. (3 tablets) three times daily after meals for two days; 1.0 mg. (2 tablets) twice daily until the desired effects were produced; then 0.5 mg. (1 tablet) twice daily as a maintenance ration. The plan was modified as circumstances required.

Rectal Administration.—After trial in two cases, the method was abandoned because of the local irritating action. The clinical result indicated that the drug was absorbed. It is possible that a preparation suitable for rectal use can be made.

DURATON OF EFFECT

This was variable. It was calculated by giving large initial doses on one or two days, then discontinuing the drug and observing the length of time necessary for the disappearance of changes in the form of the electrocardiogram (T-waves and R-T or S-T segments). It was estimated also in cases of auricular fibrillation by noting the interval

which elapsed between the last dose of urginin and the beginning of an increase in ventricular rate. The time varied, obviously, with the total amount in the body and hence with the size of the dose and the speed of its administration. Changes in the form of the electrocardiogram were observed as long as seventeen days after stopping the drug (Figs. 7 and 8 show their persistence for eleven and twelve days). Prolonged A-V conduction was recorded from seven to sixteen days after the last dose was given. In cases of auricular fibrillation, the effect on heart rate began to diminish in from three to ten days; it completely disappeared in from eight to eleven days.

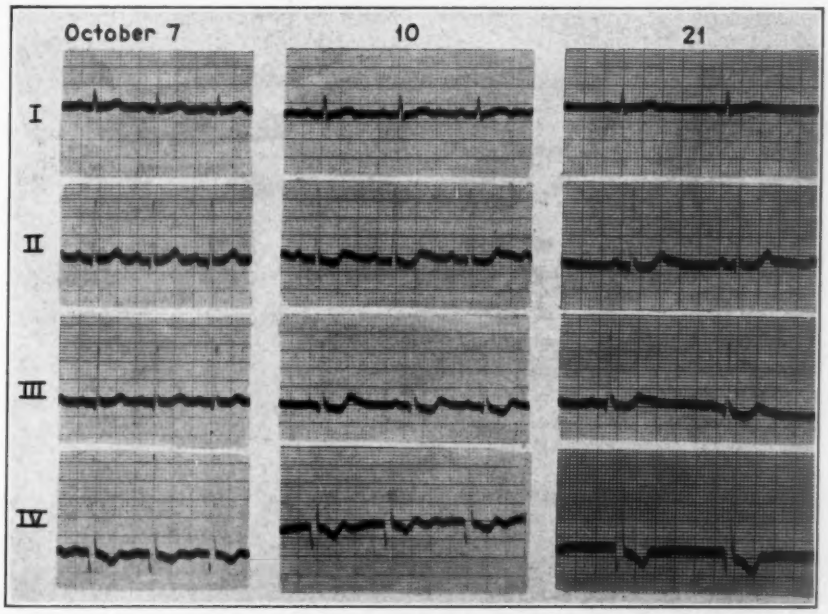

Fig. 7.—Persistence of effect of urginin on the electrocardiogram eleven days after its administration was discontinued.

Unit No. 311367. Male, aged thirty-three years. Diagnosis: Tuberculous peritonitis with ascites. (No cardiac disease.)

October 7: Control; rate 95; P-R 0.16 sec. Urginin 1.5 mg. October 8: 4.5 mg. October 9: 4.5 mg. October 10: Rate 75; P-R 0.17 sec. Record shows slowing of rate and partial inversion of T_2 and T_3; T_4 partly upright. Urginin 3 mg. October 21: Eleven days after last dose. Rate 60; P-R 0.16 sec. R-T_1 and R-T_2 still depressed; T_4 inverted.

TOXIC EFFECTS

In six patients, nausea and vomiting occurred soon after urginin was taken. Four of these were nauseated and unable to take other medication by mouth before the drug was given. Digitalis was subsequently administered to three of them and caused nausea and vomiting in each. Every patient without previous nausea was able to retain urginin if given after a meal in amounts not exceeding 1.5 mg. (3 tablets) at a time. In nine additional patients, nausea without vomiting was complained of immediately after taking the drug; in

each instance, smaller doses were tolerated without distress. Two patients had diarrhea, which ceased during continued urginin medication. Two complained of dizziness and flushing.

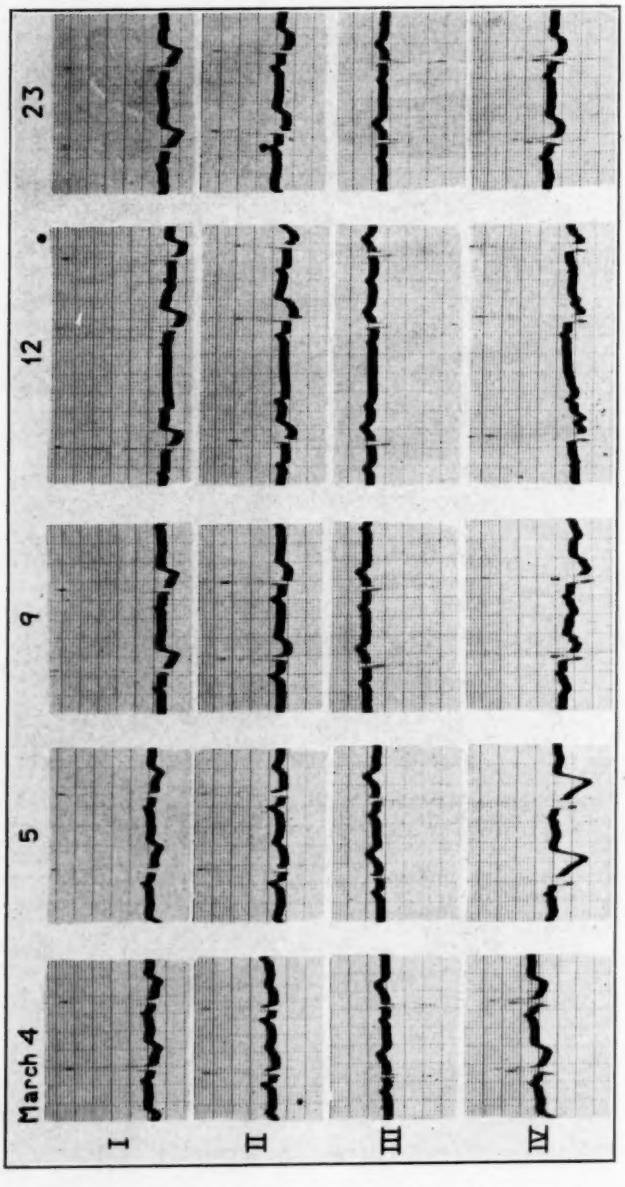

Fig. 8.—Incomplete heart-block and T-wave changes produced by urginin; persistence of latter for twelve days after the drug was discontinued.
Unit No. 46876. Male, aged forty-five years. Diagnosis: Hypertension; arteriosclerosis; cardiac hypertrophy; arteriolar nephrosclerosis.
March 4: Control; rate 75; P-R 0.15 sec. March 5: Urginin 9.5 mg. Record taken after 3.0 mg. were given. T_3 higher; T_1 deeper. March 6, 7, and 8: 2.0 mg. March 9: Rate 70; P-R 0.18 sec. T_1 more deeply inverted; $R\text{-}T_2$ depressed; T_1 diphasic and notched. Urginin 2.0 mg. March 10 and 11: Urginin 2.0 mg. On the 11th, nausea and vomiting. March 12: Incomplete heart-block with more marked T-wave changes. March 23: Twelve days after urginin was discontinued; sinus rhythm, rate 65; P-R 0.19 sec. There are still changes in the form of the T-waves and R-T segments.

One patient, nauseated by digitalis, took urginin without complaint. Another had diarrhea after taking digitalis, but none following urginin therapy.

One patient became mentally confused and had delusions of persecution after 16.5 mg. had been given during a period of eight days.

There were no changes in the electrocardiogram or other symptoms suggesting poisoning by urginin. The psychic state returned to normal several days after the drug was discontinued.

In two instances transient auricular fibrillation appeared, and in three, auriculoventricular nodal rhythm was noted following dosage which was not regarded as excessive. One case of incomplete heart-block was converted to complete block, reverting to the former rhythm three days after urginin was stopped.

To one patient, 19.0 mg. (38 tablets, containing about 81 cat units) were given intentionally over a period of seven days (Fig. 8). Vomiting and incomplete heart-block occurred simultaneously at the end of this time. Two additional tablets of 0.5 mg. each given on the following day did not cause the block to become complete, and no premature beats were observed. After the drug was stopped, vomiting continued for two days and nausea for three days. Changes in the form of the electrocardiogram persisted for at least twelve days.

Premature contractions were conspicuously absent as evidence of urginin intoxication.

No deaths could be attributed to the action of urginin.

EFFECTS ON THE ELECTROCARDIOGRAM

These were similar to the ones known to be produced by digitalis.[16] The changes observed were on rate, T-waves, R-T, and S-T segments, and on auriculoventricular conduction time. To six patients, comparable doses of urginin and of digitalis were given in succession. No appreciable differences were noted in the character of the changes produced in serial records.

In one case of auricular flutter, the auricular rate was slowed but the rhythm was not altered. Prolongation of the P-R interval was produced in six patients, incomplete A-V block in two, and complete A-V block in one. There was no effect on intraventricular conduction.

In ten patients, premature beats disappeared after medication. In eight instances these were ventricular, in one auricular, and in one junctional in origin.

SUMMARY AND CONCLUSIONS

1. A clinical study was made of the effects of urginin on 62 patients in the wards of the hospital. In those with cardiac insufficiency, urginin, administered orally, exerted an action on the heart like that of digitalis. The signs and symptoms of congestive failure tended to disappear. As a rule, edema, when present, was lost and diuresis occurred. The venous pressure fell, the circulation time decreased and the vital capacity was increased. These effects were noted in the presence of regular rhythm as well as when the auricles were fibrillating.

2. In cases of auricular fibrillation, the ventricular rate was slowed; when the rhythm was regular, slowing occurred in about one-half of the cases.

3. Diuresis and loss of weight did not occur in the absence of congestive failure.

4. The therapeutic potency of urginin, in terms of cat units, was about one-half that of digitalis. Thus, approximately two cat units of urginin were required to induce effects, both therapeutic and toxic, comparable to those induced by one cat unit of digitalis. This difference in activity may be ascribed to less complete absorption or more rapid elimination in the case of urginin.

5. A satisfactory scheme of dosage, when no digitalis or urginin had been given for at least ten days preceding, was: 1.5 mg. (3 tablets) three times a day after meals for two days; 1.0 mg. (two tablets) twice daily until the desired effects were produced.

6. The daily maintenance dose ranged from 0.5 to 2.0 mg. The average was 0.92 mg. (approximately two tablets of 1.0 mg.).

7. The total effective dose (the full amount given less 1.0 mg. theoretically excreted each day) ranged from 6.5 to 14.0 mg. The average was 9.0 mg. (18 cat units).

8. The duration of effect after therapeutic doses was variable. In cases of auricular fibrillation, the effect on ventricular rate began to diminish in from three to ten days. It disappeared completely in from eight to eleven days. Changes in the form of the electrocardiogram were observed for as long as seventeen days after the drug was discontinued. Prolonged A-V conduction was recorded from seven to sixteen days after the last dose.

9. In 6 of 62 patients, nausea and vomiting occurred soon after urginin was taken. Every patient without previous nausea was able to retain urginin if given after a meal in amounts not exceeding 1.5 mg. (three tablets). In nine additional patients, nausea without vomiting occurred; in each instance smaller doses were tolerated without distress. Other toxic effects noted were diarrhea (two cases), dizziness and flushing (two cases), mental confusion (one case), transient auricular fibrillation (two cases), auriculoventricular nodal rhythm (three cases), prolonged P-R interval (six cases), and A-V heart-block (three cases).

10. Premature beats as evidence of intoxication were not observed.

11. One patient, nauseated by digitalis, took urginin without distress. Another had diarrhea after taking digitalis, but none following urginin therapy.

12. The occurrence of any of the symptoms or signs of intoxication affords an indication for immediate cessation of therapy.

13. No deaths could be attributed to the action of urginin.

14. The effects on the electrocardiogram were similar to those seen after digitalis. The alterations noted were in the T-waves, R-T, or S-T segments, and on A-V conduction.

15. In ten patients, premature beats disappeared after medication.

16. Urginin is an effective cardiac remedy. It offers no advantages over digitalis with respect to its action in myocardial insufficiency. But it serves a purpose in that occasionally, patients in whom digitalis induces nausea, vomiting, or diarrhea are able to take urginin without suffering from unpleasant symptoms. It may be useful also when a patient harbors an unfounded prejudice against the use of digitalis.

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THE EFFECT OF THEOPHYLLINE WITH ETHYLENEDIAMINE (AMINOPHYLLINE) ON THE COURSE OF CARDIAC INFARCTION FOLLOWING EXPERIMENTAL CORONARY OCCLUSION*

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CONSIDERABLE evidence now exists that the xanthines, namely, caffeine, theobromine, and theophylline, dilate the coronary vessels and increase the coronary blood flow. This general conclusion has been derived from studies with several species of animals, the cat, dog, and rabbit, and from various types of experiments, namely, isolated strips of blood vessel,[1, 2] perfusion experiments with the isolated heart,[3, 4] heart-lung preparations,[5] and studies of coronary blood flow in the anesthetized animal.[6]

In perfusion experiments, very dilute solutions of the xanthines fail to cause coronary vasodilatation. The increase in the coronary flow seen in cases in which the drug is injected intravenously is of short duration,[6, 7] lasting only from a few minutes to about one-half an hour, corresponding to the period of the relatively high concentration of the drug in the blood stream.[8] The concentration in the blood stream after the intramuscular injection does not rise as high as directly after the intravenous injection, and as far as we know, the effect on the coronary flow of the xanthines administered orally or intramuscularly has not been determined. There is the suggestion in the recent experiments of Wiggers and Greene[9] that changes in the total coronary inflow and outflow are not necessarily accompanied by similar changes in the collateral flow to an infarcted area. None of the experimental studies on coronary flow is free of objections as evidence for the conclusion that the xanthines produce an increase in the volume of capillary flow in the heart. However, these results have served as the experimental basis on which the xanthines are advocated in the treatment of disease of the coronary arteries.

In 1935 a paper was published by Fowler, Hurevitz, and Smith[10] in which they reported that the daily oral administration of theophylline with ethylenediamine (aminophylline) in doses approximating those used therapeutically† reduces the size of the infarct resulting from the ligation of a coronary artery in the dog. They declared that clinical experience[11] was in accord with these findings[10] and suggested the use of this drug in patients with coronary thrombosis.

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†Their doses were 3 grains daily for a dog. The weights of the dogs were not stated, and on the basis of 10 to 20 kg., the dose was equivalent to about 10 to 20 grains for a man.

The suggestion that aminophylline might reduce the size of a myocardial infarct is extremely important, and their results are strongly indicative of a beneficial influence of the xanthine. The present study was undertaken to explore the possibilities further, and as a matter of practical significance, to determine whether the influence of aminophylline on the size of the infarct is a phenomenon peculiar to the dog or is applicable to other species as well. The effect of aminophylline was studied on the course of myocardial infarction resulting from coronary ligation in the cat. In this study a larger series of animals was employed, an infarct was produced the size of which could be accurately measured, and the work was carried out under conditions which excluded the possible influence of subconscious bias in the comparison of the results in control and treated animals.

The coronary circulations of the cat and the dog are essentially similar in that, in both there are extensive anastamoses between the coronary arteries and, also in both, the xanthines produce an increase in the coronary flow in perfusion experiments. Nevertheless, as will be seen, in contrast to the results reported for the dog, the xanthines were without influence on the course of the myocardial infarction in the cat.

METHOD

Various coronary arteries were ligated in 65 cats, namely, the right coronary, the descending branch of the left at various levels, the circumflex branch of the left, and also the right together with one or another of these two branches. The infarcts which proved most satisfactory for measurement resulted from ligation of the circumflex branch of the left coronary. This vessel was ligated in 52 animals, and the effect of aminophylline on the size of the infarct resulting from this operation alone was studied.

Operative Technique.—The animals were anesthetized with ether. The ether was supplied by means of a metal catheter passed through the mouth into the trachea, and through this also artificial respiration was maintained by interrupted positive pressure insufflation.

The operation was performed aseptically, tincture of iodine being used for the skin sterilization. An incision 3 to 4 cm. long was made in the left third or fourth intercostal space beginning about 0.5 cm. from the sternum. The pericardium was incised over the region of the left auricular appendage, which was held to one side to expose the left coronary artery. This was isolated at the point of its bifurcation into the descending and circumflex branches. A silk ligature was passed by means of a fine needle, and tied, around the circumflex branch at its junction with the left common coronary artery. The veins were not included in the ligature. The incision in the pericardium was left open. The thorax was closed with silk ligatures in two or three layers.

The complete operation for ligation of the left circumflex artery, from the opening to the closure of the thorax, took an average of 16.2 minutes in a series of 50 animals, with variations from 8 to 43 minutes.

Skin sutures were removed usually on the fifth day, occasionally on the fourth, sixth, or seventh day.

General Routine.—Comparable conditions for the animals of the treated and of the control series were insured by assigning to each of the two groups an approximately equal number of animals operated upon on the same day.

Daily observations were made regarding the general condition of the animal, the amount of food eaten, and the condition of the wound. The diet consisted of evaporated milk, raw chopped meat, and a canned mixed food. The animals were weighed before the operation, occasionally during, and at the end of the subsequent three-week period. An electrocardiogram was taken just prior to the operation, immediately after its completion, the following day, then every third day, and finally at the end of the experiment. At this time the blood pressure was recorded with a mercury manometer by means of a cannula inserted in the carotid artery (during local anesthesia).

Distemper was prevented by a prophylactic dose of 5 c.c. of canine antidistemper serum, injected subcutaneously at the time of operation (in 9 treated and in 9 control cats). In all but one of the remaining animals, symptoms of distemper were controlled by the injection of one or more doses of 5 c.c. of the antidistemper serum (in 4 treated and in 6 control cats).

At the end of the experiment, the animals were killed by the intravenous injection of digitalis, in order to determine the toxicity of digitalis in the presence of a myocardial infarct. The results of these observations are presented in another report.[12]

Treatment With Aminophylline.—Theophylline with ethylenediamine (aminophylline) in a 10 per cent solution was administered daily in one dose. Most of the animals received 25 mg. per kg. (calculated on the basis of the body weight before the operation) by intramuscular injection for twenty consecutive days, the initial dose being given within a few minutes after the operation. There were a few exceptions to this general plan. The first dose was 10 mg. per kg. by intravenous injection in each of two cats; in four cats the daily dose by intramuscular injection was reduced to 10 mg. per kg. during the course of treatment, so that two received 17 doses of 10 mg. per kg., one received 15 such doses, and one, two such doses.

These doses of aminophylline appeared to produce no change in the general behavior of the animal that might indicate poisoning. The toxicity of the 10 per cent solution of aminophylline was tested by intramuscular injection in several normal cats. In each of three, a dose of 50 mg. per kg. produced no appreciable effects after 16 consecutive

daily doses. A dose of 100 mg. per kg. caused vomiting, and death with convulsions after the sixth consecutive daily injection. In each of two animals, a dose of 150 mg. per kg. caused nausea and vomiting, and death after several hours.

The injections were made into the thigh muscles, using right and left alternately. The thigh muscles were sectioned post-mortem and examined for signs of irritation or infection. These appeared normal in all but one animal, in which a deep abscess had developed, first noted on the eighth day.

Post-mortem Examinations.—These were made in all cases.

The location of the ligature was established. In this way two errors were discovered in which the left common artery had been ligated, causing death within a few minutes.

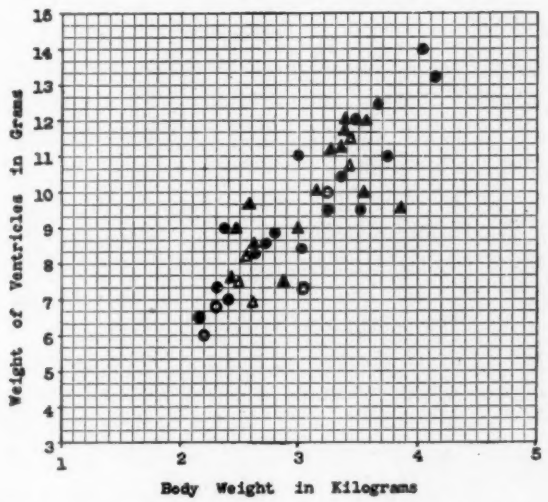

Fig. 1.—Correlation of weight of body with weight of ventricles. ▲ (treated; survived twenty-one days); △ (treated; died before twenty-one days); ● (control; survived twenty-one days); ○ (control; died before twenty-one days).

Soft adhesions often bound the margins of the incision in the pericardium partly or completely to the left auricular appendage. There were no pericardial effusions.

In no case were there adhesions between the parietal and visceral pericardium or any gross signs of pericarditis over the area of the infarction.

Intramural thrombi were absent even in cases of very extensive infarction.

The parietal pericardium, the aorta, pulmonary artery, and auricles were cut away, and the ventricles were weighed. A definite correlation between the body weight and weight of the ventricles was found to exist (Fig. 1).

After the infarct was measured, the heart was fixed in formalin and frozen sections from several areas were stained with hematoxylin and eosin for microscopic examination.

Serious secondary infection did not occur. Of the 42 cats used as the basis for this study, mild secondary infections at the site of the wound occurred in 12 animals (in four treated animals and eight controls). Stitch abscesses only were present in nine of these, and had completely healed before the end of the experiment.

Coronary Circulation in the Cat.—In each case the right and left coronary arteries and their main branches were dissected out, their relative sizes noted, and a sketch was made of their distribution, especially on the posterior wall of the heart. Usually the left circumflex artery was larger than the right circumflex. The left circumflex usually was found to give off one or more branches on the anterior wall of the left ventricle, then turn posteriorly and run across the upper border of the left ventricle, giving off in its course several branches to the auricle and to the posterior wall of the left ventricle, with its terminal branches lying close to the interventricular sulcus on the posterior surface of the heart. Sometimes the terminal branches extended for a considerable distance into the wall of the right ventricle. On the other hand, occasionally the right circumflex vessel was very much larger than the left, and sent branches to supply a fairly large portion of the posterior wall of the left ventricle. Marked differences in the size of the infarcts could often be directly related to manifest differences in the relative size of the right and left circumflex vessels. For example, in one animal, ligation of the right coronary artery produced a small infarct involving only the posterior wall of the left ventricle midway between the base and the apex. In this case the right coronary artery supplied most of the posterior wall of the left ventricle, and the left circumflex vessel was exceedingly small.

Fig. 2 shows a sketch of the circulation and the infarct in the average animal.

The Infarct.—The infarct was examined before and after the chambers of the heart were opened. After ligation of the left circumflex artery, the location and form of the infarct were fairly uniform, although the size varied considerably. It involved chiefly the posterior wall of the left ventricle, and all layers of the wall. It was irregularly triangular in shape with the base along the auriculoventricular border. It narrowed toward the apex, terminating above the posterior surface of the apex in the average-sized infarct, and involved the posterior papillary muscle. In the larger lesions, the infarct extended around to the anterior surface of the apex, to the anterior papillary muscle, along the posterior border of the septum, and in seven cases it involved a narrow strip of the right ventricle adjacent to the involved septum.

The infarct was readily recognized by the color and the thinning of the ventricular wall. Infarcted areas about a week or ten days old were fairly thick, yellow, and inelastic. Those about three weeks old showed marked thinning of the wall and atrophy of the papillary muscle; they were reddish and slightly lighter in color than the surrounding musculature, and, usually, showed some yellowish mottling. The boundary was less distinct in the older infarcts, although in all it was fairly clearly defined.

Measurement of Infarct.—The boundaries of the infarct were often more clearly defined and somewhat larger on the endocardial surface of the ventricle than on the outer surface. The opened ventricle was laid out flat, the area of the infarct outlined in India ink on the endo-

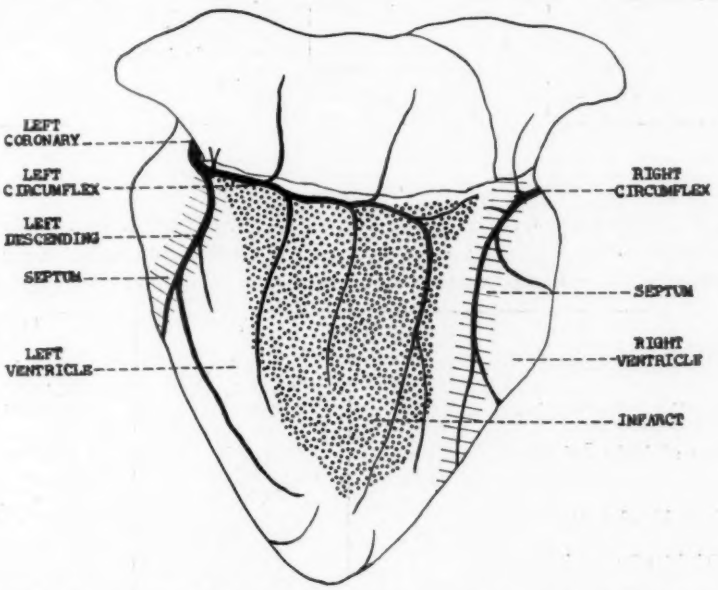

Fig. 2.—Dorsolateral view of heart. Note usual coronary circulation, site of ligature on left circumflex artery, and location, size, and shape of average infarct.

cardial surface, and a contact tracing of the area was made on a ground glass plate. In some cases a contact reproduction of the inked outline on the heart was made directly on tracing paper, and in still others, a direct contact paper cut was made. The areas of the infarcts, reproduced independently by two workers using the same specimen, agreed within 8 per cent. An estimate of the relative sizes of the infarcts was made by inspection, and the exact size of the tracings or cuts was measured by the planimeter.

An attempt was made to correlate the weight of the ventricles with the size of the infarct. No definite relationship was revealed by this relatively small series. The scatter of the points, however, was found to be essentially similar in the control and the treated groups (Fig. 3).

TABLE I

CAUSE OF DEATH IN 21 ANIMALS THAT FAILED TO SURVIVE THE THREE-WEEK PERIOD AFTER LIGATION OF THE LEFT CIRCUMFLEX ARTERY

DURATION OF LIFE AFTER LIGATION	NO. CATS	CAUSE OF DEATH	REMARKS
A few minutes	1	Hemorrhage	Tear in myocardium
A few minutes to a few hours	9	Acute effects of infarction	Unusually large vessel
5 to 14 days	6	Pneumonia	One unusually large infarct; others of average size
18 days	1	Distemper	
6 days	1	Cardiac failure?	Pulmonary edema, peritoneal and pleural serosanguineous effusion; very large infarct
8 days	1	Cardiac failure	Subcutaneous edema; pleural and peritoneal effusions; very large necrotic infarct
4 days	1	Ether	During operation on infected foot
8 days	1	Undetermined	Infarct of average size

TABLE II

RESULTS IN ANIMALS TREATED WITH AMINOPHYLLINE AND IN CONTROLS WHICH SURVIVED THREE WEEKS AFTER LIGATION OF LEFT CIRCUMFLEX ARTERY

	CONTROL GROUP	TREATED GROUP
Number of cats	17	14
Averages for groups		
Initial body weight	3.12 kg. (2.15-4.15)	3.09 kg. (2.40-3.55)
Duration of operation	14.0 min. (8-43)	19.2 min. (10-22)
Loss of body weight	11.8% (Loss of 34.9—gain of 7.2)	13.0% (Loss of 33.3—gain of 7.3)
*Mean blood pressure	156 mm. (133-183)	145 mm. (120-170)
Weight of ventricles	9.9 gm. (6.5-14.0)	9.9 gm. (7.5-12.0)
Size of infarct	0.82 sq. in. (0.35-1.47)	0.95 sq. in. (0.45-2.00)
R-T segment displacement		
Marked	64.7%	64.3%
Doubtful	23.5%	21.4%
None	11.8%	14.3%
Per cent of those with marked displacement which disappeared before three weeks	45.4%	44.4%
Average duration of displacement in those returning to normal before three weeks	16.4 days	15.5 days
Degree of healing of infarct on microscopic examination		
Advanced	18.8%	7.7%
Moderate	56.2%	61.5%
Slight	25.0%	30.8%

*Averages based on 13 cats in each group.

Blind Test.—The blind test was applied to that part of the work which involved judgments. The description of the animal's appearance at the end of the three-week period was made by one to whom the identity of the animal as a control or one which had received aminophylline was unknown. The outlining of the area of the infarct and its reproduction, as well as the classification of the microscopic sections, were also conducted under similar conditions.

RESULTS

Of the 52 animals in which the circumflex branch of the left coronary was ligated, 9 died of the acute effects of the infarction, and 12 died of other causes in less than three weeks. The causes of death in these are presented in Table I.

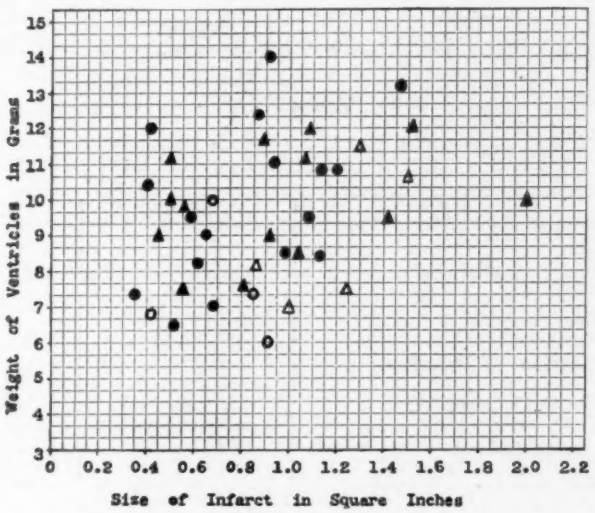

Fig. 3.—Lack of correlation of size of infarct with weight of ventricles. Symbols are as in Fig. 1.

Table II shows the results obtained in 31 animals which survived the three-week period. Of these, 17 served as controls and 14 were treated with aminophylline. The two groups are almost identical in respect to those factors which might have a bearing on the size of the resulting infarct, namely, the general condition of the animal, the body weight, the weight of the heart, the state of the animal's nutrition as judged by the change in body weight, and the blood pressure.

The average body weight at the beginning was 3.12 kg. in the controls, and 3.09 kg. in the treated group. The majority of the animals were indistinguishable from normal and some weighed more at the end of the three-week period than at the start. The average change was a loss of 11.8 per cent of the original body weight in the controls and 13 per cent in the treated series.

The mean blood pressure averaged 156 mm. of mercury in the control series, and 145 mm. in the treated series.

The average weight of the heart was 9.9 gm. in both groups.

The average size of the infarct was 0.82 square inches in the control, and 0.95 in the treated group. Those treated with aminophylline, therefore, had developed an infarct which on the average was 18.3 per cent larger than those which had not received the drug. This difference would be increased if the area of involvement of the right ventricle had been included. This area, present in three of the treated group and in one of the controls, could not be measured on the endocardial surface of the heart by the method we employed. It is difficult to understand how aminophylline could have acted to make matters worse, and it is possible that a difference of this magnitude may be accidental.

The eleven animals which survived the operation but died before the end of the three-week period showed essentially similar results (Table III).

TABLE III

RESULTS IN ANIMALS TREATED WITH AMINOPHYLLINE AND IN CONTROLS WHICH LIVED MORE THAN TWENTY-FOUR HOURS, BUT DIED BEFORE THREE WEEKS

	CONTROL GROUP	TREATED GROUP
Number of cats	6	5
Averages		
Duration of life	9.5 days (4-17)	7.6 days (5-12)
Body weight	2.64 kg. (2.27-3.23)	2.91 kg. (2.57-3.43)
Duration of operation	18.5 min. (8-34)	13.0 min. (10-17)
Weight of ventricles	7.5 gm.* (6.00-10.0)	8.6 gm. (6.9-11.5)
Size of infarct	0.82 sq. in. (0.41-1.14)	1.18 sq. in. (0.87-1.50)

*The ventricles were weighed in only 4 animals of this group.

An analysis of the electrocardiograms was made and some of the results are summarized in Table II. Changes in the T-waves were not considered reliable, because they occur spontaneously in unanesthetized cats,[13] and were seen quite frequently in a series of animals in which the same operation was performed except for the ligation of the coronary artery, in connection with another study. Prolongation of conduction time above the control (amounting to 0.03 second or more) occurred* in 8 of the 23 controls and in 5 of the 19 treated animals. These changes usually appeared immediately after the operation, although in some cases they were not present until a day or two later, and in all cases they were transient. The significance of the changes in conduction is uncertain under the conditions of these experiments. The tracings of the treated and of the control groups were compared with regard to displacements of the R-T segments and the incidence of ventricular tachycardia. The

*Animals of Tables II and III are considered in these figures.

chief change of the R-T segment was elevation* above the base line in all three leads or in Leads II and III only, and in all cases in which it occurred it was present immediately after the operation. The frequency of an elevated R-T segment seen postoperatively before any treatment, was substantially the same in both groups, namely, about 88 per cent of the control group and 86 per cent of the group which was to be treated, and the degree of elevation was also similar in both (Table II). Aminophylline, 10 mg. per kg., injected intravenously in

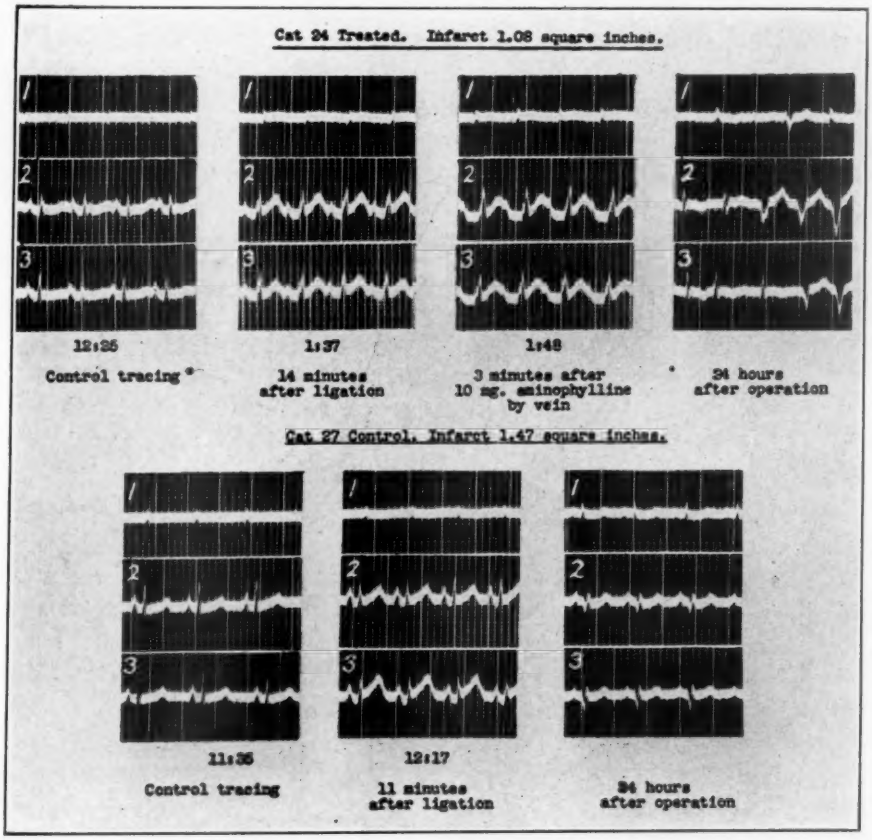

Fig. 4.—Typical electrocardiograms after ligation of circumflex branch of left coronary. Note similar displacement of R-T segment and recovery in twenty-four hours for both control and treated animals, and absence of effect of aminophylline on R-T segment displacement.

two instances, within a few minutes after the ligation did not reduce the displacement of the R-T segment (Fig. 4). Treatment did not shorten the time required for the R-T segment to return to normal, namely, about sixteen days in each group. An observation having a similar significance is the fact that the numbers which failed to show complete return of the segment to the base line at the end of the three-week period

*Due consideration was given to the fact that in control tracings the R-T segment is sometimes elevated about 0.5 to 1 mm. above the base line.

were equivalent in the two groups. Ventricular tachycardia occurred much more frequently in the treated group (9 of 19 cases, or 47.4 per cent of the treated animals, and 2 of 23 cases, or 8.7 per cent of the controls), although the incidence of this disorder before any treatment was negligible (one in the treated group and two in the controls). This abnormal rhythm appeared in two and eight days respectively, in the control group, and in the other group, during treatment for from two to twenty-one days, averaged six days. This is the second unfavorable factor which has appeared in the treated group. It is apparently not due to the fact that this group had the larger infarcts, for the cases of ventricular tachycardia were dispersed throughout the whole range of size of infarcts, from among the smallest to the largest. This difference may also be purely accidental.

A series of 68 sections from different regions of the hearts, including the center of the infarct, the area of transition and the adjacent musculature, were examined microscopically. Three sections were selected as standards to represent three grades of healing of the infarct:

Slight (large amount of necrotic tissue, relatively few round cells and fibroblasts, and little or no collagen deposition);

Moderate (little or no necrotic tissue, a relatively loose arrangement of round cells and fibroblasts, and an early stage of collagen deposition); and

Advanced (no necrotic tissue whatever, a dense, compact arrangement of round cells and fibroblasts, and an advanced stage of collagen deposition).

With this as a basis of comparison, 29 sections taken from the center of the infarcts were classified independently by each of two of the workers, and without knowledge of their identity as sections from treated or control animals. The results of this comparison show that the microscopic appearance of the infarcts in treated and untreated animals cannot be distinguished (Table II). Photomicrographs of sections showing advanced and slight degrees of healing for typical members of both groups are reproduced in Fig. 5.

SUMMARY AND CONCLUSIONS

The present study in cats (19 treated and 23 control) shows that daily treatment with fairly large doses of aminophylline does not exert any influence that can be considered favorable on the course of the infarction resulting from ligation of a large coronary artery, namely, the circumflex branch of the left vessel.

Intensive treatment with this drug for three weeks was without influence on the systemic blood pressure, or on the course of the electrocardiographic changes. Furthermore, it did not accelerate the process of healing, nor did it reduce the size of the infarct.

The results of this study are therefore not in agreement with those which have been reported for the dog. It should be noted that, in addition to factors which have already been indicated, these studies differ with respect to the species of animal and also the vessel ligated. It seems possible that the influence of the collateral circulation after ligation of the entire left circumflex branch may be different from that

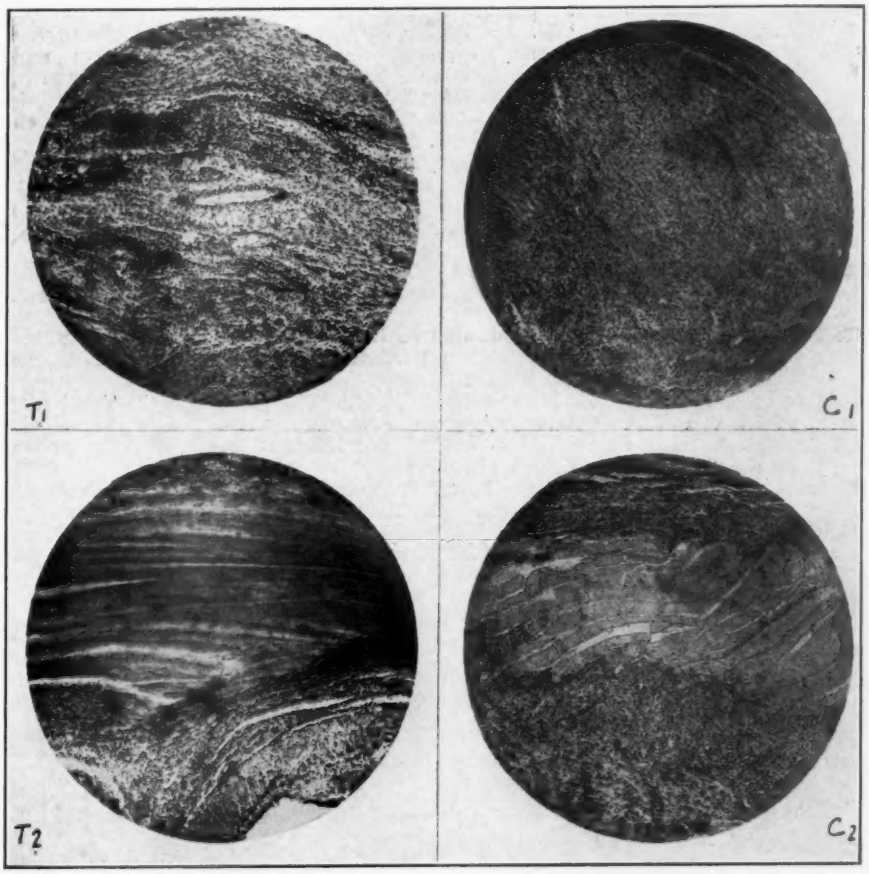

Fig. 5.—Photomicrographs of sections of typical infarcts in both control and treated animals showing advanced and slight degrees of healing in each group at the end of three weeks.

C-1 (control, advanced healing); C-2 (control, slight healing).
T-1 (treated, advanced healing); T-2 (treated, slight healing).

after ligation of a portion of the left descending branch, and that this may in part account for the difference in results obtained.

In any case, the routine use of aminophylline in the treatment of coronary thrombosis receives no support from the results of these experiments. This conclusion is in accord with the results of the recent clinical study by Gold, Kwit, and Otto,[14] which shows that the xanthines are without beneficial influence on the course of pain in angina pectoris.

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THE SIGNIFICANCE OF AN ABSENT OR A SMALL INITIAL POSITIVE DEFLECTION IN THE PRECORDIAL LEAD*

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INTRODUCTION

IN RECENT years the value of the precordial lead as an aid in the diagnosis of myocardial damage, and particularly of infarction, has been well established. The significance of absence of the initial positive deflection or Q-wave has been emphasized in many of the reports dealing with the precordial lead. In hundreds of normal controls cited in the literature[1-15] this wave has never been absent and as a rule has measured more than 2 mm., although occasionally a deflection as small as 1 mm. has been noted. On the other hand Wolferth and Wilson and their coworkers[16-21] have found the initial positive deflection frequently absent in coronary occlusion, clinical and experimental, with infarction of the anterior surface of the heart. This did not hold for posterior infarction. Wood et al.[3] later reported that it was rarely absent in other conditions, such as bundle-branch block and advanced myocardial disease without coronary occlusion. Bohning and Katz[11] found a small initial positive deflection frequently in coronary sclerosis. Recently, Levine and Levine[22] have reviewed the precordial lead in coronary disease with particular attention to the initial positive deflection. Their post-mortem observations showed that not only was absence of this deflection nearly always associated with myocardial infarction but also that infarction was present in one-half of the patients with an initial positive deflection measuring 2 mm. or less. They concluded, therefore, that the absence of this deflection was indicative of myocardial infarction and assumed this to be present in patients with angina pectoris even when there was no history of coronary thrombosis. Moreover, these authors almost always encountered an absent or small initial positive deflection in bundle-branch block in the absence of myocardial infarction.[23] In a series of cases of coronary occlusion analyzed by Jervell[29] the initial positive deflection was absent only when there was recent or old infarction of the anterior surface of the left ventricle.

METHOD AND DATA

At the Mount Sinai Hospital the precordial lead has been taken routinely in addition to the standard leads since 1934. Our interest

*From the Cardiographic Laboratory, Mount Sinai Hospital.

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in the significance of the initial positive deflection in the precordial lead was aroused early by finding it absent or small in several cases without myocardial damage or with damage not associated with coronary artery disease. Furthermore, the relative significance of an absent and a small initial positive deflection was uncertain. We have therefore analyzed the electrocardiograms obtained in 4,500 consecutive patients between April, 1934, and October, 1936, with particular attention to the initial positive deflection.

The chest lead was taken by the method previously described by us.[9, 15] The right arm electrode was placed over the precordium just within the apex, in the fourth or fifth interspace, and the left leg served as the site of the indifferent electrode. By this method positivity of the precordial electrode is represented by a wave directed downward, and negativity by a wave directed upward, the opposite of that which obtains in the standard leads. The precordial electro-

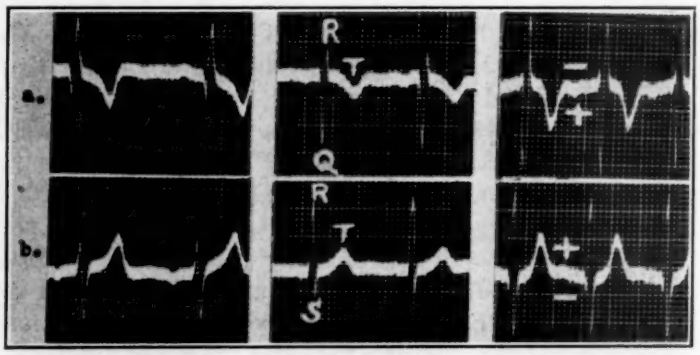

Fig. 1.—Three examples of normal precordial lead. *(a)* Recorded in the customary manner so that negativity of the precordial electrode is represented by an upward deflection. The old nomenclature is given—an initial downstroke Q, followed by the intrinsic deflection R. In the third example there is a small initial upward deflection preceding the Q. The T-wave is inverted. *(b)* Recorded so that negativity of the precordial electrode is represented by a downward deflection. New nomenclature—an initial upward deflection R, and an intrinsic deflection S. In example three there is a small Q. The T-wave is upright.

cardiogram thus obtained (Fig. 1*a*) consists of an initial downward positive deflection (Q-wave) followed by an upward negative deflection (R-wave); the T-wave is inverted. Since the introduction of the precordial lead into routine use, it has been suggested by some[6, 10, 12, 13, 24, 29] including the senior author,[9] that the polarity of the circuit be reversed so that the direction of the waves would conform to that in the standard leads. This is accomplished by attaching the left leg lead wire to the precordial electrode and the right arm lead wire to the indifferent electrode. The QRS complex then consists of an initial positive upward deflection, the R-wave, followed by a negative downward intrinsic deflection, the S-wave and the T-wave is upright (Fig. 1*b*). Not infrequently a small negative deflection precedes the R-wave which is called Q-wave. Recently, Wilson[21] maintained that this arrangement

is theoretically more correct and has advocated the change. It is our belief that it will be adopted by other workers in the near future. In order to avoid confusion until this is done, in this paper the components of the QRS group will be referred to respectively as the initial positive deflection (Q-wave of old technique, R-wave of new) and the intrinsic negative deflection (R-wave of old technique, S-wave of new).

In 64 patients the precordial lead was also studied with the precordial electrode placed at five different positions on the chest wall. Position 1 was two cm. to the right of the right sternal line in the fourth interspace; position 2 was in the midsternal line; position 3 was two cm. to the left of the left sternal line in the fifth interspace; position 4, just within the cardiac apex; position 5, outside the apex. In these 64 patients, furthermore, the "neutral point" or "zero potential" method, advocated by Wilson et al.[19] and Kossman and Johnston,[13] was employed to determine if it possessed any practical advantage over the ordinary procedure described above. The comparative results obtained will be discussed later.

ANALYSIS OF CASES WITH ABSENT INITIAL POSITIVE DEFLECTIONS

The initial positive deflection was absent in 120 (2.7 per cent) of the 4,500 consecutive patients in whom precordial leads were taken. Seventy-nine of these (66 per cent) were known to have sustained a coronary occlusion, recent or old; in the remainder (34 per cent) no such history could be elicited nor did the clinical course suggest the presence of coronary occlusion. A perusal of Table I shows that in all but two of the cases of coronary occlusion there was infarction of the anterior wall of the heart or a combination of anterior and posterior wall infarction (Figs. 2, 3). Two cases were considered to present infarction of the posterior wall alone, since each presented the typical electrocardiographic pattern (Q_2, T_2; Q_3 T_3) (Figs. 4, 15) and in one, post-mortem examination revealed thrombosis of the right coronary artery with posterior infarction. However, in this case there was also an old partial occlusion of the left anterior descending artery. While no evidence of infarction was found on the anterior wall it is possible that it had formerly been present, which might explain the absence of the initial positive deflection. Thus when the initial positive deflection of the precordial lead was absent in coronary thrombosis, the standard leads nearly always showed a Q_1 T_1 pattern and necropsy revealed infarction of the anterior surface of the heart.

In the group of 41 patients with an absent initial positive deflection but without a definite clinical history of coronary thrombosis, 27 exhibited unequivocal clinical or electrocardiographic evidence of myocardial damage associated with arteriosclerotic heart disease or long-standing hypertension. Only three of these patients came to

post-mortem examination but all showed recent or old coronary occlusion with anterior or both anterior and posterior wall infarction. Although many of the remaining 24 patients had never had precordial pain, and those with angina pectoris had never had a major attack which could be interpreted as a coronary occlusion, a previous silent or gradual coronary closure could not be definitely ruled out in view of the marked cardiac damage present in these cases and of the post-mortem findings in the above three cases. In these 24 patients, there-

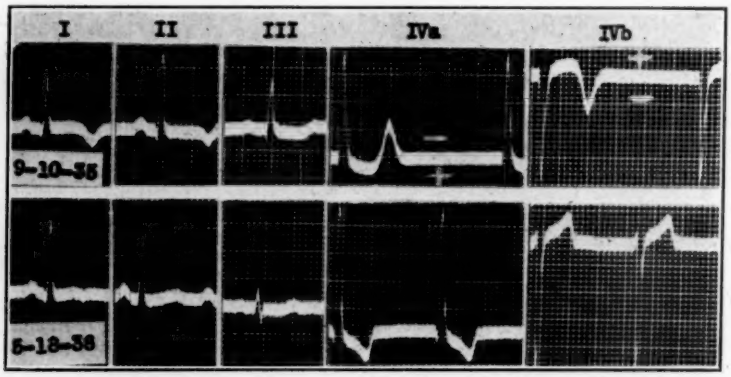

Fig. 2.—Acute coronary thrombosis (anterior wall infarction). Male, aged forty years. Sept. 10, 1935. One week after the attack. The standard leads show coveplane T_1 and T_2. In the precordial lead the T-wave is directed oppositely to the normal and the initial positive deflection is absent. This is the typical appearance in anterior wall infarction. May 18, 1936. The standard leads are returning to normal although T_1 still is semi-inverted. T_4 has become normal. The initial positive deflection has reappeared but is small. This small deflection may be the only remaining abnormality following coronary occlusion.

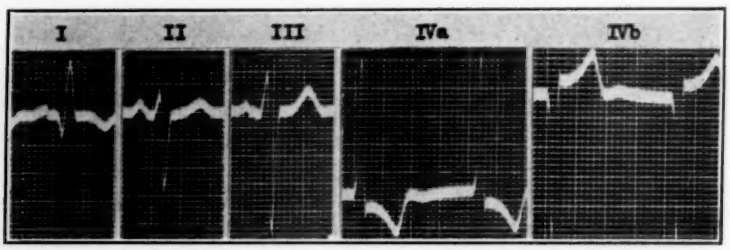

Fig. 3.—Old coronary thrombosis. Male, aged sixty years. Post-mortem examination shows an old occlusion of the left anterior descending coronary artery with an aneurism of the left ventricle. The standard leads show marked LVP, large Q_1 and inverted T_1, characteristic of anterior wall infarction. The only abnormality in the precordial lead is absence of the initial positive deflection.

fore, it is possible that the absence of the initial positive deflection represented unrecognized myocardial infarction, as Levine and Levine[22] believed to be the case in their patients with angina pectoris. On the other hand, we have seen this finding present in patients with advanced coronary sclerosis,[3] bundle-branch or intraventricular block[3, 22, 23] or only an enlarged left ventricle[25] in the absence of coronary thrombosis. It may be that the absence of the initial posi-

tive deflection in our group can be explained in this way, for the majority had marked enlargement of the heart as a result of long-standing hypertension and the standard lead electrocardiogram often showed a typical hypertensive pattern, that is, marked left ventricular preponderance, high voltage and T_1 inversion (Fig. 5). Still others showed marked intraventricular conduction defects and occasionally bundle-branch block (Fig. 6). Additional post-mortem examinations are necessary to settle this point.

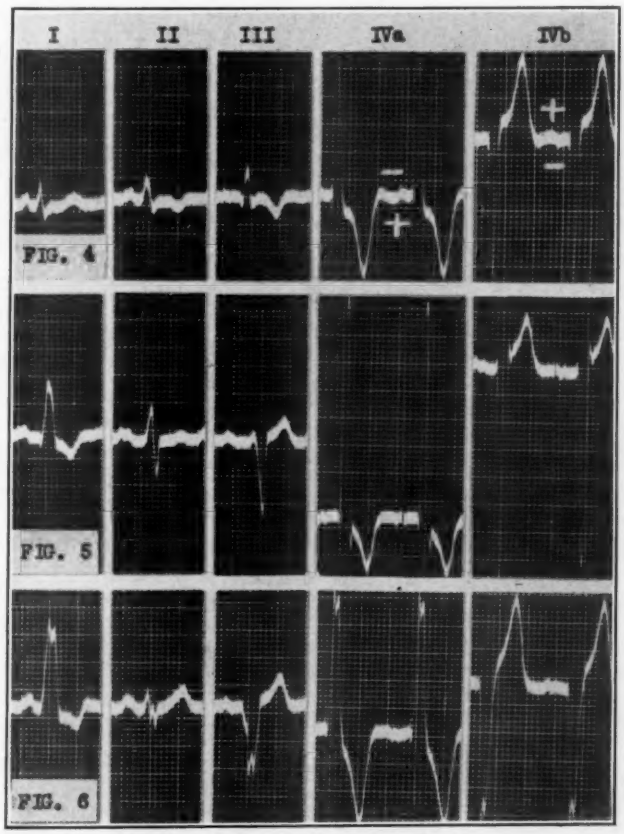

Fig. 4.—Recent coronary thrombosis. Male, aged sixty-two years. Standard leads show T_2 T_3 pattern characteristic of a posterior wall infarction. The precordial lead shows almost complete disappearance of the initial positive deflection. The T-wave is of high amplitude but of normal direction.

Fig. 5.—Calcific aortic stenosis. Male, aged fifty-five years. At post-mortem examination the left ventricle was enormously hypertrophied and the heart weighed 1,050 gm., but the coronary arteries were normal. The standard leads are characteristic of enlargement of the left ventricle. The initial positive deflection in the precordial lead is extremely small. Note the huge negative intrinsic deflection. The T_4 is normal.

Fig. 6.—Essential hypertension. Female, aged fifty-two years. No history or clinical evidence of previous coronary occlusion. Left bundle-branch block with a small to absent initial positive deflection in the precordial lead.

Absent Initial Positive Deflection in Cases Without Infarction.—There remain 14 patients with absence of the initial positive deflection in which the diagnoses were miscellaneous (Table I). The presence of

myocardial infarction in this group was most improbable, because of the comparative youth of the patients as well as the clinical course. These cases were diagnosed acute or chronic nephritis, 4; rheumatic cardiovalvular disease, 3; syphilitic heart disease, 2; spontaneous pneumothorax, 2; acute myocarditis of unknown etiology, 1; thyrotoxic heart disease, 1; and severe anemia, 1. The patients with acute nephritis were aged fifteen, twenty-seven, and forty years respectively. There was no clinical evidence of coronary disease although definite electrocardiographic changes were present (Figs. 7, 8). The latter are common during the course of acute glomerulonephritis and have

TABLE I

ANALYSIS OF 120 CASES OF ABSENT INITIAL POSITIVE DEFLECTION

CLINICAL DIAGNOSIS (120 CASES)	POST-MORTEM (15 CASES)
79 old or recent coronary occlusion	12 old or recent myocardial infarction
69 anterior (Q_1 T_1 type)	8 anterior wall infarction with LAD occlusion
2 posterior (Q_3 T_3 type)	1 posterior wall infarction with right coronary and old partial LAD occlusion
8 anterior and posterior	3 anterior and posterior wall infarction with LAD and right coronary occlusion
41 no history or clinical signs of coronary thrombosis	
27 arteriosclerotic or hypertensive heart disease	3 old or recent coronary thrombosis with anterior wall infarction with LAD occlusion
14 miscellaneous diagnoses 3 rheumatic cardiovalvular disease 2 cardiovascular syphilis 3 acute nephritis 1 chronic nephritis 1 acute myocarditis, unknown etiology 2 spontaneous pneumothorax 1 thyrotoxic heart disease 1 severe anemia	

already been reported by us.[26] These changes are transient, including absence of the initial positive deflection, and may be explained on the basis of myocardial involvement as a result of diffuse capillary damage which occurs in acute glomerulonephritis.

In two instances of spontaneous pneumothorax the initial positive deflection was absent and in two others it was very small. In all four there was definite displacement of the mediastinum as seen on roentgenogram and the standard lead electrocardiogram revealed a peculiar axis deviation apparently due to rotation of the heart (Fig. 9). In three cases, absorption of the pneumothorax, with re-expansion of the collapsed lung and return of the mediastinum to its usual position, was accompanied by a return to normal of the electrical axis and of

the initial positive deflection. It is thus evident that rotation or displacement of the mediastinum, in the absence of cardiac disease, may not only distort the electrical axis in the standard leads, as already demonstrated by one of us,[28] but may also cause disappearance or marked diminution in size of the initial positive deflection of the precordial lead.

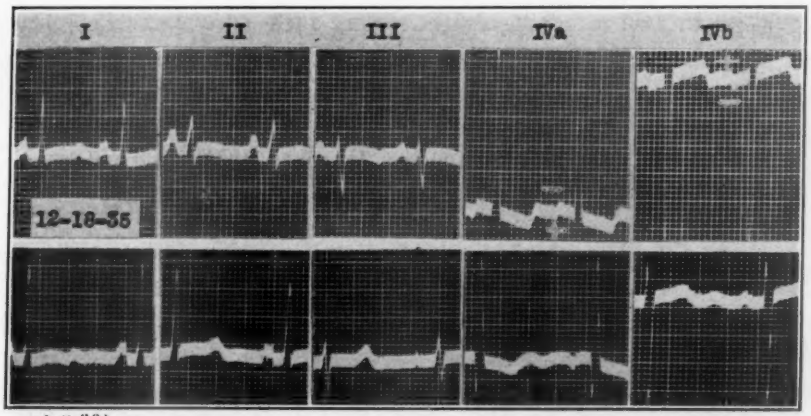

Fig. 7.—Acute glomerulonephritis. Male, aged twenty-seven years. Dec. 18, 1935. Flat T-waves in standard leads. In the precordial lead the initial positive deflection is absent and the T-wave is diphasic. Jan. 8, 1936. T_1 has become inverted, T_2 and T_3 are normal. The initial positive deflection has reappeared and T_4 is normal.

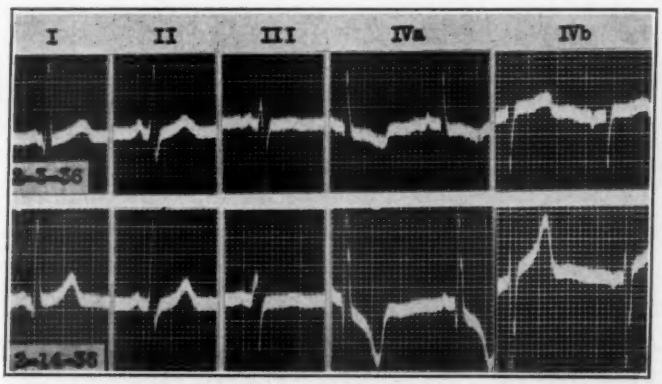

Fig. 8.—Acute glomerulonephritis. Male, aged sixteen years. Feb. 3, 1936. Standard leads normal except for LVP. The only definite abnormality present is absence of the initial positive deflection in the precordial lead. Feb. 14, 1936. Standard leads are unchanged. The initial positive deflection of the precordial lead has reappeared and T_4 is of higher amplitude.

Three other patients in this miscellaneous group were males, aged thirty-five, thirty-six, and thirty-nine years respectively, who suffered from chronic rheumatic valvular disease. Two of these had aortic insufficiency with marked left ventricular preponderance and a large left ventricle (Figs. 10 and 12) and one had mitral stenosis with right ventricular preponderance and a large right ventricle (Fig. 11). These three

cases emphasize again that a large heart may lead to disappearance of the initial positive deflection in the absence of myocardial infarction.

Summary.—It is seen that absence of the initial positive deflection in the precordial lead nearly always signifies myocardial involvement. In two-thirds of the cases of this series it was due to myocardial infarction involving the anterior surface of the heart, very rarely the posterior wall. It may be absent also in patients with conditions other than myocardial infarction or coronary sclerosis, such as glomerulonephritis,

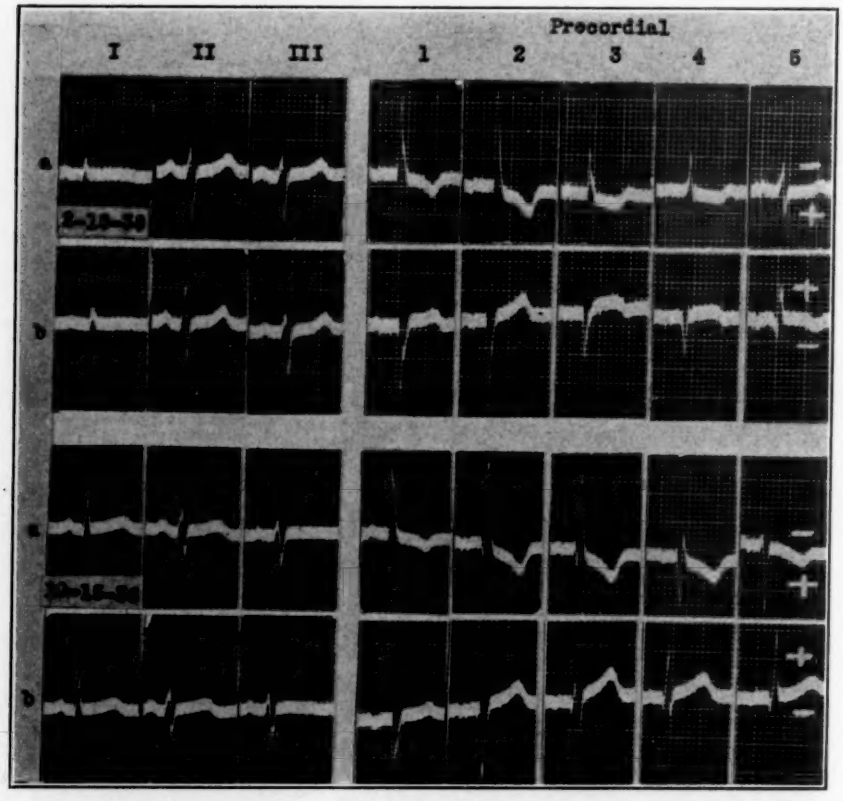

Fig. 9.—Tension pneumothorax, left side. Male, aged twenty-one years. Feb. 18, 1936. The standard leads show an unusual electrical axis due to rotation and displacement of the heart. The precordial lead shows absence of the initial positive deflection in all positions on the chest wall. The T-wave is diphasic in positions 3, 4, and 5. Oct. 15, 1936. Almost complete absorption of the pneumothorax. The heart has returned to the normal position. There is now left axis deviation. The initial positive deflection has reappeared in all positions except position 1. The T-wave is normal.

(Position 1 is two cm. to the right of the right sternal line. Position 2 is at the midsternum. Position 3 is two cm. to the left of the left sternal line. Position 4 is just within the apex. Position 5 is outside the apex.)

rheumatic and syphilitic heart disease, intraventricular block. Finally, rotation or displacement of an otherwise normal heart may produce disappearance of the initial positive deflection.

QRS of Unusual Form (M and W-shaped QRS).—In 24 patients included in the group with an absent initial positive deflection the QRS

complex of the precordial lead was of an unusual form (Figs. 13, 14, 15). This type of QRS group was often widened and consisted of a large initial negative wave followed by a more or less large positive wave and frequently a second negative wave (W or M type). Bohning and Katz[11] pointed out the frequency of such a QRS group in patients with coronary sclerosis or intraventricular block. In the majority of cases we found this type of ventricular complex to have the same significance as that in which the initial positive wave was absent and only a large negative wave present. In recording the precordial lead in these patients in the five positions on the chest wall described pre-

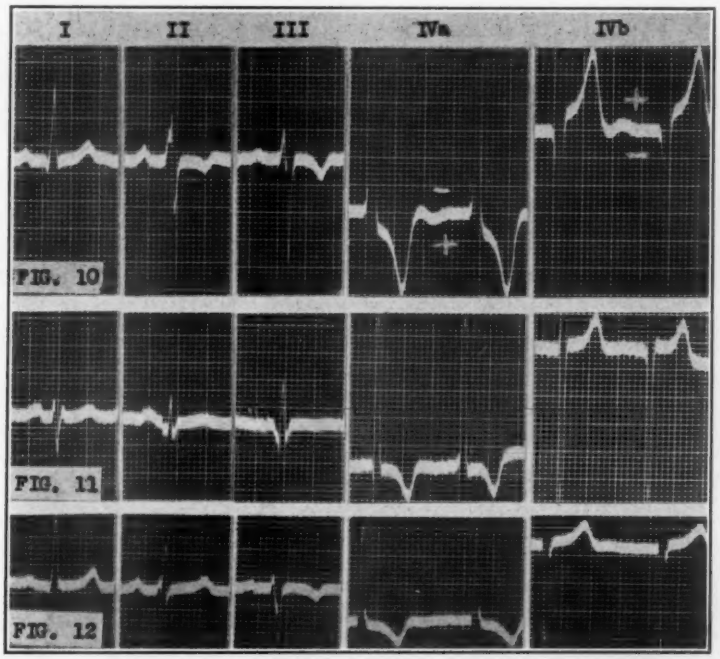

Fig. 10.—Chronic rheumatic valvular disease, aortic insufficiency. Male, aged thirty-six years. Left ventricle markedly enlarged. Standard leads show marked LVP and inversion of T_2 and T_3. The initial positive deflection in the precordial lead is absent and the T_4 is of high amplitude.

Fig. 11.—Chronic rheumatic valvular disease, mitral stenosis. Male, aged thirty-seven years. Enlarged left auricle and right ventricle. The standard leads show marked RVP. The initial positive deflection in the precordial lead varies from small to absent. The T_4 is normal.

Fig. 12.—Chronic rheumatic valvular disease, mitral stenosis, and aortic insufficiency. Male aged twenty-one years. Standard leads show only LVP and T_3 inversion. The initial positive deflection is extremely small. The T_4 is normal.

viously, it was noted that when an M or W-shaped QRS was present in the routine position (just within the apex), the ordinary type of complex with an absent initial positive deflection frequently appeared in the other positions on the chest wall (Figs. 13, 14, 15). Thus when an abnormal QRS of this type is observed in the routine precordial lead, one should repeat the electrocardiogram obtaining records from

the various positions across the chest. This procedure will usually demonstrate an absent initial deflection in one or more of these positions. Occasionally there was observed a transition from an M-shaped QRS to a monophasic QRS in the same record, probably due to different phases of respiration (Fig. 16). All the patients presenting this abnormal type of QRS had marked myocardial disease and 15 of the 24 had suffered a coronary occlusion. Wilson and his coworkers[20, 21] have suggested that an M or W-shaped QRS group appears when only the inner layers of the ventricular wall are infarcted or when the precordial electrode is placed over the edge of an area of infarction.

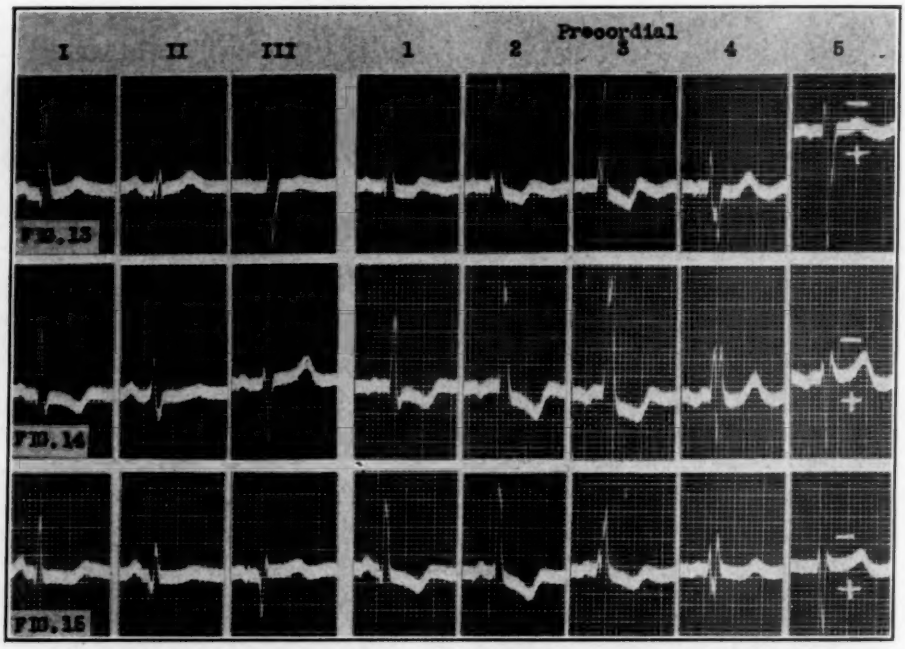

Fig. 13.—Coronary thrombosis two years previously (anterior wall infarction). Male, aged forty-nine years. Standard leads present residual Q_1 and W-shaped QRS in Lead II. The QRS complex in the routine precordial lead (position 4) is of an abnormal type (R-S type) and the T-wave is directed opposite to the normal. Other positions (1, 2, 3) show absence of the initial positive deflection.

Fig. 14.—Coronary thrombosis two years previously (anterior wall infarction). Male, aged fifty-nine years. Standard leads show Q_1 T_1 pattern. The QRS in the routine precordial lead (position 4) is M-shaped and the T-wave is opposite to the normal. In positions 1, 2, and 3 the initial positive deflection is absent.

Fig. 15.—Coronary thrombosis two years previously (posterior wall infarction). Male, aged forty-nine years. Standard leads show Q_2 Q_3 pattern. Routine precordial lead (position 4) shows M-shaped QRS and an abnormal T-wave. The initial positive deflection is absent in positions 2 and 3.

When the electrode is moved toward the center of the infarct the QRS will become of the usual type with a single negative deflection.

Permanence of Absence of the Initial Positive Deflection.—Eighty-three patients with an absent initial positive deflection had repeated electrocardiograms; in 14 of these the positive deflection reappeared.

This group comprised 11 patients suffering from recent coronary thrombosis (Figs. 2, 18, 19), two from acute nephritis (Figs. 7, 8) and one from spontaneous pneumothorax (Fig. 9). In four of the patients with coronary thrombosis the deflection which reappeared remained small (Fig. 2). The time of reappearance varied considerably, the shortest interval being three days and the longest, one year. However, these figures are not precise since the electrocardiograms were not always taken at regular intervals. The reappearance of this deflection was not always associated with changes in the standard leads,

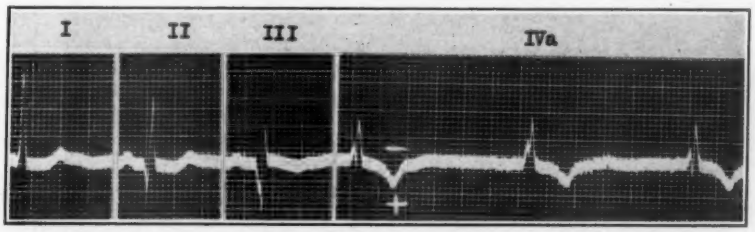

Fig. 16.—Old coronary thrombosis two years previously (posterior wall infarction). Male, aged sixty years. Standard leads show Q_2 Q_3 T_3 pattern. The precordial lead shows an abnormal M-shaped QRS which varies in appearance from beat to beat. In the second beat the initial positive deflection is seen to be absent.

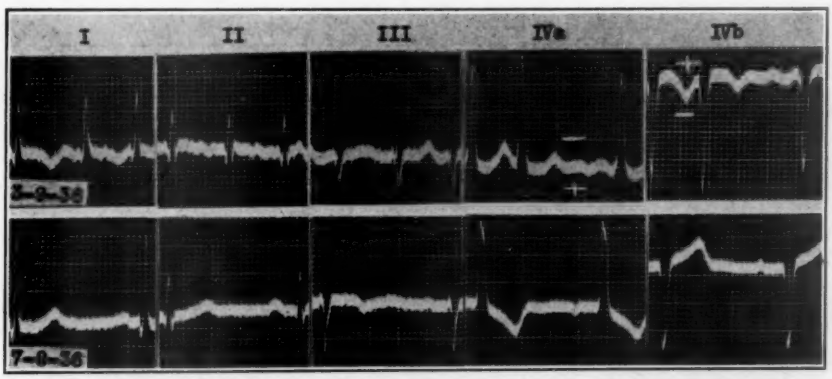

Fig. 17.—Recent coronary thrombosis (anterior wall infarction). Female, aged fifty years. Mar. 9, 1936. Three weeks after acute attack. Standard leads show auricular fibrillation, small Q_1 and inversion of T_1. In the precordial lead which is characteristic of anterior infarction the initial positive deflection is absent and the T-wave is directed opposite to the normal. July 8, 1936. Four months later. The standard leads have returned to normal except for the small Q_1. The T_4 has also become normal but the initial downward deflection is still absent. This is the only remaining sign of previous infarction.

for in several cases the latter remained abnormal (Figs. 18, 19). Nor did this wave reappear in every case in which definite clinical improvement occurred. In many of the cases of coronary thrombosis observed since 1934, it has remained absent until the present time despite disappearance of clinical symptoms and of many of the abnormalities in the standard leads (Figs. 13, 17). Similar observations were reported by Wood and his associates.[3]

Correlation of Absent Initial Positive Deflection With Abnormal T-wave.—In somewhat over half the cases an absent initial positive deflection was accompanied by an abnormal T-wave, that is, one of negative polarity (upright T-wave of old terminology) (Figs. 2, 17). Nearly all these (82 per cent) were cases of coronary thrombosis. The presence of both of these abnormalities is therefore characteristic of

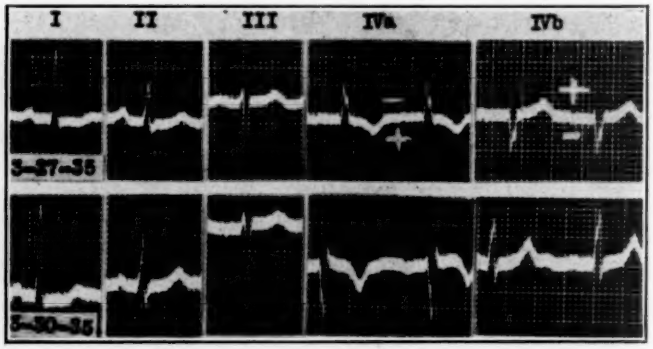

Fig. 18.—Acute coronary thrombosis. Female, aged fifty-nine years. Mar. 27, 1935. Three days after the acute attack. Standard leads show LVP and diphasic T_1. The initial positive deflection is very small. T_4 is normal. Mar. 30, 1935. No change in the standard leads. The initial positive deflection has returned to normal within three days.

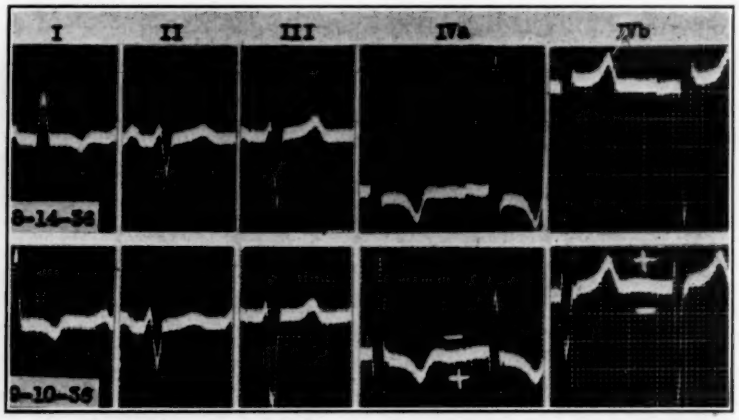

Fig. 19.—Acute coronary thrombosis (anterior wall infarction). Male, aged forty-eight years. Aug. 14, 1936. One week after the acute attack. The standard leads show marked LVP. Intraventricular conduction defect and T_1 inversion. The initial positive deflection of the precordial lead is absent but T_4 is normal. Sept. 10, 1936. No change in the standard leads. The initial positive deflection has reappeared within one month.

anterior wall infarction. On the other hand 46 per cent of cases with absent initial positive deflection presented a normal T-wave, that is, one of positive polarity; while myocardial involvement was present in all of these, only nine had infarction (Figs. 3, 19). In the latter cases the absent initial positive deflection was the only sign in the precordial lead of infarction. Occasionally there was very little abnormality

even in the standard leads, particularly following recovery from an attack of thrombosis (Fig. 17). Moreover in several cases of recent coronary thrombosis the initial deflection remained absent or small long after an abnormal R-T transition or T-wave had returned to normal (Figs. 2, 17). As Wilson et al.[17] have already pointed out, the QRS changes following myocardial infarction are more permanent than the T-wave changes. Our own observations corroborate this, for only in a small percentage of cases did the initial positive deflection reappear after one to two years.

ANALYSIS OF CASES WITH SMALL INITIAL POSITIVE DEFLECTION

In addition to absence of the initial positive deflection a study was made of those cases in which, while present, it measured only 2 mm. or less. One hundred and seventy-five or 3.9 per cent of the 4,500 patients studied showed this finding. Nearly all these patients (92.5 per cent) had definite clinical or electrocardiographic evidences of myocardial involvement. In only 13 patients (7.5 per cent) was the heart presumably normal.

Eighty-four per cent of the patients with a small initial deflection showed abnormalities in the three standard leads indicative of myocardial damage. Bundle-branch block occurred in 11 per cent and a definitely enlarged heart in over one-half of the cases. Analysis of the clinical and pathological diagnoses in the 175 cases revealed the following (Table II): 51 (29 per cent) had recent or old coronary thrombosis (Figs. 2, 18); 65 (37 per cent) had coronary artery disease with or without hypertension; 25 (14 per cent) had chronic rheumatic valvular disease (Figs. 5, 11, 12). The remaining 21 cases included essential hypertension, chronic pulmonary disease, subacute bacterial endocarditis, acute and chronic nephritis, syphilitic aortitis, thyroid heart disease, paroxysmal tachycardia, and Libman-Sacks' disease. The 13 patients (7.5 per cent) without any clinical or electrocardiographic signs of cardiac involvement were admitted with the following diagnoses: mild essential hypertension, spontaneous pneumothorax, obesity, hypoplastic heart, thyroiditis, myasthenia gravis, infectious arthritis, and psychoneurosis.

It is thus seen that an initial positive deflection in the precordial lead measuring 2 mm. or less is almost always definitely abnormal and in the vast majority of instances is observed in patients with myocardial involvement, usually associated with coronary sclerosis with or without thrombosis. A small initial deflection may be the only abnormality found in the precordial lead, even when the standard leads present definite abnormalities, including T-wave changes (Figs. 2, 5, 11, 12, 18). Thus in only 35 cases (20 per cent) was the small initial positive deflection accompanied by an abnormal T-wave in the pre-

cordial lead. This is in contrast with an incidence of 54 per cent in patients with an absent deflection. Similarly, the incidence of coronary thrombosis in the former group was smaller, that is, only 40 per cent. Yet, it is our feeling that in the cases of coronary thrombosis the small initial positive deflection was just as significant as the abnormal T-wave. The importance of a small initial positive deflection

TABLE II

ANALYSIS OF 175 CASES WITH SMALL INITIAL POSITIVE DEFLECTION

CLINICAL DIAGNOSIS (175 CASES)	POST-MORTEM (26 CASES)
50 recent or old coronary thrombosis	14 recent or old coronary thrombosis 2 anterior wall infarction 4 posterior wall infarction 8 anterior and posterior infarction
66 arteriosclerotic or hypertensive heart disease	1 recent and old coronary thrombosis (posterior infarction) 6 coronary sclerosis
25 rheumatic valvular disease	2 rheumatic valvular disease (mitral and aortic)
7 chronic pulmonary disease	
3 essential hypertension with abnormal electrocardiogram	
6 miscellaneous heart disease	
2 subacute bacterial endocarditis	1 subacute bacterial endocarditis in syphilitic aortic insufficiency
1 Libman-Sacks' disease	1 atypical verrucous endocarditis with myocarditis
1 syphilitic aortitis	
2 paroxysmal tachycardia	
5 miscellaneous disease	
1 chronic nephritis	
2 acute nephritis	
1 colloid goiter	
1 myxedema	
13 no heart disease	
2 obesity	1 flabby heart but normal myocardium
4 essential hypertension with normal hearts	
2 spontaneous pneumothorax	
1 hypoplastic heart	
1 thyroiditis	
1 myasthenia gravis	
1 infectious arthritis	
1 psychoneurosis	

is further emphasized by the observation that it may frequently disappear entirely for several beats and then reappear (Figs. 8, 11). As this was usually a phasic change it was probably dependent on the respiratory movements of the heart. Furthermore, a small deflection not infrequently disappeared when the precordial electrode was shifted a few centimeters on the chest wall. Thus a sharp separation of absent or very small initial positive deflections was not always possible.

Very little importance has been attached to the height of the intrinsic negative deflection* in the precordial lead since it may vary so

*Upward R-wave of old technique, downward S-wave of new.

much in normal records; it may be very large or very small (Fig. 1). However, some useful information may be gathered from correlation of the amplitude of the two deflections of the QRS. It was found that nearly all the patients with a small initial positive deflection and no evidence of heart disease had an intrinsic deflection measuring not more than 10 mm. The patients with coronary thrombosis usually had a large intrinsic deflection in the presence of a small initial deflection. Thus the significance of the latter is greater when the amplitude of the succeeding deflection is above 10 mm. For example, an initial positive deflection of 1.5 mm. appears less significant to us when the intrinsic negative deflection is 7 mm. than when it is 17 mm. Again, an initial positive deflection of 2 mm. with an intrinsic deflection less than 10 mm. is equivocal, but if the latter is 20 mm. or more we are certain that such an initial positive deflection is abnormal. Hence in doubtful cases it is wise to correlate the amplitude of the two deflections of the QRS group.

VARIATION IN SIZE OF THE INITIAL POSITIVE DEFLECTION

It is well known that the QRS complex in the precordial lead shows variations in amplitude in repeated records. This has been attributed to slight inescapable changes in the position of the precordial electrode. We therefore investigated the records of 92 patients with a small initial positive deflection on whom repeated electrocardiograms were obtained at varying intervals. In 71 of these this deflection remained 2 mm. or less in all records, although minor variations in size did occur. In the other 21 cases it varied back and forth from small to normal in serial records. In these 21 cases there was no correlation between changes in the size of the initial positive deflection and the amplitude of the succeeding negative deflection. It is possible that in many of these patients the variations were associated with changes in the heart muscle, for the patients included cases with coronary thrombosis and progressive coronary artery disease. In some, however, a change in the position of the electrode was probably the cause.

In 42 of the cases with a small initial positive deflection which had repeated electrocardiograms there were noted also variations in the amplitude of the intrinsic negative deflection. Yet in none of these did the former become greater than 2 mm. even when the latter doubled in size. We may conclude therefore that abnormal initial positive deflections may remain small, independent of change in the amplitude of the intrinsic deflection.

THE INITIAL POSITIVE DEFLECTION IN CORONARY THROMBOSIS; CLINICAL CORRELATION

Since absence of the initial positive deflection (absent Q_4 of previous authors) has been emphasized as a diagnostic electrocardiographic sign of myocardial infarction, we have made a particular

study of this deflection in a large series of coronary thrombosis. In Table III we have arranged 261 consecutive cases of recent and old coronary thrombosis and have correlated the site of infarction with the presence or absence of this deflection. In 128 patients with infarction of the anterior surface of the heart, diagnosed by a typical electrocardiographic pattern (Q_1 T_1 type), the initial positive deflection in the precordial lead was absent in slightly more than half the cases, small in one-sixth and normal in about one-third. In 78 patients with infarction of the posterior wall (Q_3 T_3 type), it was normal in all but 11 cases; in 9 of these it was small and in only two was it absent. In 30 patients with signs of infarction of both anterior and posterior surfaces no clear cut division was found; the initial positive deflection was normal, small or absent, depending apparently upon which lesion exerted the predominant effect on the form of the electrocardiogram. It is noteworthy, however, that the frequency of absence of the initial positive deflection when the anterior and pos-

TABLE III

THE INITIAL POSITIVE DEFLECTION IN CORONARY THROMBOSIS (261 CASES)

LOCATION OF INFARCTION	NO. OF CASES	INITIAL POSITIVE DEFLECTION		
		ABSENT	SMALL	NORMAL
Anterior wall	128	71 (55.0%)	19 (15.0%)	38 (30.0%)
Posterior wall	78	2 (2.5%)	9 (11.5%)	67 (86.0%)
Anterior and posterior	30	9 (30.0%)	13 (43.0%)	8 (27.0%)
Undetermined location	25	0	10 (40.0%)	15 (60.0%)
Total	261	82 (31.0%)	51 (19.5%)	128 (49.0%)

terior surfaces of the heart were involved was much smaller than when the infarction was limited to the anterior wall. An absent initial positive deflection in coronary thrombosis with but two exceptions (Fig. 15) occurred only when the anterior surface of the heart was damaged, whether this was the sole injury or whether the posterior wall also was involved. A small deflection, however, occurred almost as frequently in posterior as in anterior wall infarction (Fig. 4).

INITIAL POSITIVE DEFLECTION IN CORONARY THROMBOSIS; POST-MORTEM CORRELATION

The above conclusions were corroborated by the observations in 50 patients with coronary thrombosis in whom post-mortem examination was made (Table IV). There were 15 patients with anterior wall infarction; the initial positive deflection was absent in eleven, small in two and normal in the remaining two. In 13 patients with posterior wall infarction it was small four times and absent only once. However in the latter case the absent deflection may have resulted from an old partial occlusion of the left anterior descending coronary artery which was also present. When infarction of both anterior and

posterior walls was found (19 cases) the initial positive deflection was absent only four times and small in one-half of the cases. Again we note the smaller incidence of absence of the initial positive deflection when anterior wall infarction is accompanied by posterior wall infarction. Perhaps the latter sets up an electrical effect which balances that of the former, so that the QRS complex remains normal. In two cases of infarction of the lateral wall of the left ventricle and in one case of septal infarction without involvement of the anterior surface, the standard lead electrocardiogram showed a typical T_1 T_2 pattern but a normal QRS was present in the precordial lead. It is thus evident that in coronary thrombosis absence of the initial positive deflection almost invariably denotes infarction of the anterior wall. However a normal initial positive deflection not infrequently occurs in the presence of infarction in this site, particularly when the posterior surface of the heart is involved simultaneously.

TABLE IV

THE INITIAL POSITIVE DEFLECTION IN ACUTE CORONARY THROMBOSIS
(50 POST-MORTEM CASES)

LOCATION OF INFARCTION	NO. OF CASES	INITIAL POSITIVE DEFLECTION		
		ABSENT	SMALL	NORMAL
Anterior wall	15	11 (73.3%)	2 (13.3%)	2 (13.3%)
Posterior wall	13	1 (8.0%)*	4 (31.0%)	8 (61.0%)
Anterior and posterior wall	19	4 (21.0%)	9 (47.5%)	6 (31.5%)
Lateral wall (left ventricle)	2	0	0	2
Anterior septum	1	0	0	1
Total	50	16 (32.0%)	15 (30.0%)	19 (38.0%)

*Plus old partial thrombosis of left anterior descending without anterior wall infarction.

SMALL INITIAL POSITIVE DEFLECTION; POST-MORTEM OBSERVATIONS

It has already been shown that when the initial positive deflection is small, clinical or electrocardiographic evidence of myocardial damage is usually present. In our opinion, a small initial positive deflection is almost as significant as an absent one, and the post-mortem observations in 26 patients with this finding (Table II) support this view. Fifteen of these showed evidence of myocardial infarction, recent or old. However, in contrast to an absent initial positive deflection, a small one did not tend to localize the infarction to the anterior surface. In only two of these fifteen patients was the infarction limited to the anterior wall; in five it was solely posterior; and in eight, both anterior and posterior. Of the eleven patients without infarction ten showed definite myocardial involvement due to coronary sclerosis or to valvular disease. In only one was the heart muscle normal. Levine and Levine[22] similarly found myocardial infarction in one-half of a group of fifteen patients with a small initial deflec-

tion examined post mortem. The post-mortem observations of these authors and our own lead to the conclusion expressed previously that a small initial positive deflection nearly always indicates myocardial involvement and usually is associated with recent or old coronary thrombosis, whatever the site of infarction.

SIMPLE CHEST ELECTRODE VERSUS "ZERO POTENTIAL" LEAD

Recently Wilson and his associates[19] and Kossman and Johnston[13] have employed the so-called "zero potential" lead to exclude any possible effects of the indifferent electrode. They pair the precordial electrode with a central terminus which is connected through three large and equal resistances to both arms and left leg. They regard the potential of this terminus as practically zero throughout the cardiac cycle and the curve obtained to represent the potential variations of only the precordial electrode. These investigators point out that the potential of the left leg which is the site of the indifferent electrode may be great enough to alter the appearance of the precordial lead. Thus it is claimed that if the initial positive deflection is small when the precordial lead is obtained by the ordinary method, it may at times be absent if the "zero potential" method is used. This may be theoretically correct but actually we found little difference when the precordial lead was recorded with both methods in the same patient.

In 28 cases with a normal QRS group in the precordial lead, the latter was taken in the five positions over the chest wall as previously described, with both the "zero potential" and the ordinary simple electrode. Although slight differences in voltage were observed, in no instance did a normal initial positive deflection become small or disappear when the lead was recorded by the Wilson technique. Similarly, no change occurred in 9 patients with myocardial damage in whom this deflection was small. A few variations, however, were found in a group of 27 patients with an absent initial positive deflection. In five instances the "zero potential" lead presented a small instead of absent deflection in all or some of the chest positions. The diagnoses in these 5 patients were respectively recent coronary thrombosis, old coronary thrombosis, rheumatic aortic insufficiency, spontaneous pneumothorax, and acute myocarditis of uncertain etiology.

It appears to us from these observations that the "zero potential" possesses no diagnostic advantage over the routine method, so far as the initial positive deflection is concerned. The greatest change, from an absent to a very small deflection, was not common. Furthermore, the significance of a very small deflection is almost as great as that of an absent one.

CAUSE OF ABSENT INITIAL POSITIVE DEFLECTION

Wilson and his associates[16-21] believe that absence of the initial positive deflection is due to the presence of an area of dead or inactive tissue on the anterior surface or apical region of the heart. They, as well as Bellet and Johnston,[4] have demonstrated that absence of the initial positive deflection was a constant late finding in direct and indirect leads from a dog's heart after ligation of the left anterior descending coronary artery. They attributed this to the fact that since the infarcted area no longer responded to the stimulus there was no difference in potential between the endocardial and epicardial surfaces. The electrocardiogram therefore resembled one obtained by leading off directly from the ventricular cavity in which the QRS group consists only of a large negative deflection. Levine and Levine[22] agreed that absence of the initial positive deflection was nearly always due to myocardial infarction but did not explain its absence in their cases of bundle-branch block and pericarditis. On the other hand, Frucht[25] believed that enlargement of the left ventricle, by causing rotation of the heart, could produce absence of this deflection. However, because of his lack of post-mortem evidence and since the initial deflection frequently remains normal in spite of considerable cardiac enlargement, this view has not been accepted. Our results tend to show that both these factors, anterior wall infarction and cardiac rotation or enlargement, may be significant. Obviously in the cases of pneumothorax there was no myocardial involvement, but the hearts were definitely rotated and displaced. When the cardiac axis returned to normal, the QRS group in the precordial lead also became normal. Furthermore, the cases of rheumatic valvular disease in young individuals with a large heart and absent or small initial deflection cannot be explained on the basis of myocardial infarction. Similarly in acute nephritis we have shown[26, 27] that there are no gross anatomical changes in the myocardium and the absence of the initial positive deflection must be explained on the basis of capillary damage. Nevertheless, we agree with Wilson that in the great majority of instances the cause for disappearance of this deflection is myocardial infarction.

What has been said of an absent initial positive deflection applies also to a small one. The conditions associated with absence of this wave may cause instead a marked diminution in its size. Indeed, a small deflection may at times disappear and reappear in the same record. Therefore a small initial deflection probably has a significance similar to that of an absent one.

SUMMARY

1. The initial positive deflection in the precordial lead (Q-wave of old, R-wave of new technique) was absent in 2.7 per cent of 4,500 consecutive hospital patients and was small (2 mm. or less) in 3.9 per cent.

2. In two-thirds of the patients, absence of this deflection was associated with recent or old coronary thrombosis and anterior wall infarction, and in one-fifth, with coronary artery disease alone, with or without hypertension.

3. The initial positive deflection was also absent in 14 cases diagnosed as acute and chronic glomerulonephritis, rheumatic and syphilitic valvular disease, pneumothorax, Graves' disease, and acute myocarditis. There was no evidence of myocardial infarction in these cases.

4. In patients with an M or W-shaped QRS complex precordial leads obtained from other positions on the chest wall usually demonstrated absence of the initial positive deflection. This holds frequently when a large initial negative deflection precedes a large positive deflection.

5. Absence of this deflection was permanent in the majority of cases even when an abnormal T_4 and abnormal standard leads returned to normal.

6. Absence of the initial positive deflection was accompanied by an abnormal T_4 in 54 per cent of cases.

7. Of the patients with a small initial positive deflection 7.5 per cent had no clinical evidence of cardiovascular disease. The remainder suffered from coronary thrombosis (29 per cent), coronary artery disease with or without hypertension (37 per cent), rheumatic valvular disease (17 per cent), miscellaneous heart involvement (12 per cent). These included cases of intraventricular or bundle-branch block.

8. In only one-fifth of these patients was there an associated abnormal T-wave in the precordial lead. A small initial positive deflection was significant when followed by an intrinsic deflection of at least 10 mm.

9. In a large group of cases with anterior wall infarction, diagnosed electrocardiographically or at autopsy, the initial positive deflection was absent in more than one-half, small in one-sixth, and normal in one-third. In posterior wall infarction this deflection was rarely absent but was frequently small.

10. In 26 patients with a small initial positive deflection, myocardial infarction was found 15 times. Only one case showed normal heart muscle.

11. Comparison of the ordinary method of recording the precordial lead with the "zero potential" method of Wilson revealed no practical advantage of the latter as far as diagnosis was concerned.

CONCLUSION

The precordial lead has become increasingly important in electrocardiographic diagnosis, not only in coronary thrombosis but also in involvement of the heart in other conditions. It is not infrequently abnormal when the standard leads appear normal. The most significant

change in the precordial lead is absence of the initial positive deflection which may occur even when the T-wave remains normal. An absent initial positive deflection is the most reliable sign of myocardial infarction and, with rare exceptions, localizes the infarct in the anterior wall of the heart. Although it reappears in a small number of cases, it usually remains absent permanently and may be the only electrocardiographic sign of previous infarction. A small initial positive deflection may have the same significance as an absent one; however, it is less specific than the latter and does not indicate the site of infarction. It is nearly always an abnormal finding.

Hitherto the relation of the absence of the initial positive deflection to coronary thrombosis alone has been considered important. However, this study emphasizes the significance of an absent or small deflection in various other diseases which lead to damage of the myocardium or to enlargement or change in position of the heart. Therefore, while an abnormal initial positive deflection is, in most cases, indicative of myocardial infarction, it should no longer be regarded as pathognomonic of this condition.

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SOME EFFECTS OF ALTERATION OF POSTURE ON ARTERIAL BLOOD PRESSURE*

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THAT gravity has an influence on the distribution of blood in the body has long been recognized and most of the fundamental points are brought out in the papers of Hill,[1] and Hill and Barnard.[2] References to the earlier literature (Priory, 1826, Hall, 1832, and others) are found in these papers of Hill. These earlier observers found, for example, that if a dog or man were bled in the vertical position until syncope occurred, then recovery followed on placing the subject in a horizontal position. Hill, however, carried out a very comprehensive set of experiments on rabbits, cats, dogs, and monkeys which showed, among other things, that the force of gravity must be regarded as a cardinal factor in dealing with the distribution of the blood; that the important duty of compensating for the simple hydrostatic effects of gravity in changes of position must be ascribed to the splanchnic vasomotor mechanisms; that the amount of compensation depends largely upon individual differences; that the compensation is far more complete in upright animals, such as the monkey, than in rabbits, cats, or dogs, and therefore is probably far more complete in man; that in some normal monkeys overcompensation for the hydrostatic effect occurs; that in the normal monkeys and man, gravity exerts but little disturbing influence, owing to the perfection of the compensatory mechanism; that when the power of compensation is damaged by paralysis of the splanchnic vasoconstrictors, induced by severe operative procedures or by injuries to the spinal cord, by asphyxia, or by some poison such as chloroform or curare, then the influence of gravity becomes of vital importance; that the feet-down position is of far greater moment than the feet-up position, because when the power of compensation is destroyed, the blood drains into the abdominal veins, the heart empties, and the cerebral circulation ceases; that firmly bandaging the abdomen prevents the drop of pressure when the animal is turned feet down; that if the heart is affected, as by chloroform or curare poisoning, the restoration of pressure is incomplete; that vagus inhibition and the cardiac acceleration are subsidiary compensatory mechanisms in the feet-up and the feet-down positions respectively; that chloroform rapidly paralyzes the compensatory vasomotor mechanism and damages the heart; that ether, on the other hand, only paralyzes the compensatory vasomotor mechanism very slowly and when pushed in enormous amounts; that chloroform can, by destroying the compensation for gravity, kill the animal if

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it be placed with abdomen at a lower level than the heart but that elevation or compression of the abdomen immediately compensates for the vasomotor paralysis produced by chloroform.

Since the taking of blood pressure on man became a common procedure a number of studies on the effects of changing posture in man have been made which will be referred to later. In such experiments the blood pressure was taken in one position and then again after the change. There was usually about a minute or more between the readings. Now Hill's tracings show the adjustments are very rapid and that much can occur in a minute. It seemed desirable, therefore, to obtain information about changes occurring in man in short intervals of time. In the arrangements we have used we can get three or four readings of blood pressure in a minute and are therefore better able to follow the adjustments.

THE MEASUREMENT OF BLOOD PRESSURE

There are various factors to be considered in the measurement of blood pressure; such as the experimental error of the observer, and the instrumental error of the sphygmomanometer. In all of the work done here the Tycos self-recording sphygmomanometer was used. The bag was attached to the upper arm and the arm not moved in its relation to the thorax during the course of the experiment. This machine was thoroughly tested and the results obtained indicated that the blood pressures measured upon it are entirely comparable, within the range of normal, to those taken by the more common auscultatory methods. The advantages of this instrument are: some elimination of the personal error in the measurement of blood pressure since the recordings are mechanical, and the possibility of making rapidly repeated measurements of blood pressure—as many as three or four per minute—merely by moving the writing stylus on the same chart. The instrumental error in this type of machine is relatively small, averaging about 2 to 4 mm. Hg. The conditions of the experiment were kept as nearly the same for different subjects as possible.

One point which is generally not considered in the taking of blood pressure is the effect of the painful stimulus resulting from congestion in the arm. In order to reduce this to a minimum, the cuff should be inflated as rapidly as possible to a point 20 to 30 mm. Hg above the expected systolic blood pressure, and the deflation started immediately upon the completion of inflation. This was accomplished by means of a simple apparatus as follows: Compressed air is led into a large (8 liter) bottle provided with two outlets. One outlet is attached to an adjustable mercury valve so that the pressure may be kept at any desired level in the bottle. A tube provided with a stopcock connects the other outlet of the bottle to the arm cuff. The cuff is inflated practically instantaneously by turning the stopcock. By this quick inflation there is virtually

no venous congestion and thus less pain and unpleasantness. As soon as the cuff is inflated the stopcock to the pressure bottle is closed and the deflation of the cuff started immediately.

In our experience at least three trials were found to be necessary before a subject became sufficiently accustomed to the experimental procedure to show cardiovascular measurements at a basic level. There was always a certain amount of excitement present in the first trials which showed chiefly in the high pulse rate.

Our own work on the change in posture may be divided into three parts. (1) The immediate effect, i.e., during the first minute; (2) the prolonged effect after the first minute; (3) experiments on animals trying to determine the mechanisms of adjustments.

1. Immediate Effects

When the Subject Stood Up.—These changes were studied by allowing the subject first to rest in the reclining position until the blood pressure became stable. This usually did not take longer than five minutes. The subject was then told to stand up with as little effort as possible, and a series of blood pressure records was taken rapidly. The accuracy of the recording sphygmomanometer depends on adjusting the apparatus to the heart rate. The heart rate always increases on standing. In the first trials the recumbent and standing rates were determined and the machine set at the expected standing rate. The first systolic record was obtained about ten seconds after the change in position had taken place, the second systolic record at about twenty to thirty seconds after the change, and the third systolic record forty-five to sixty seconds after the change. The diastolic records appeared some five to ten seconds after the corresponding systolic records. This procedure was carried out on a good number of normal individuals, chiefly medical students, nurses, and instructors.

The results obtained on persons with normal pressures may be seen graphically in Figs. 1 and 2. Fig. 1 shows the resulting reaction on systolic pressure of 14 individuals. In this chart the vertical lines indicate thirty-second intervals while the horizontal lines represent 10 mm. of mercury pressure. The values for the three readings after the changes are indicated and the points joined. We have no proof that the blood pressure exactly followed these lines.

With one exception the first systolic record after the change was lower than the reclining systolic pressure, the amount of the drop varying in different individuals from 5 to 40 mm. Hg. After the initial drop the curves are different as may be seen from the charts. Within thirty seconds the majority of the subjects had a systolic pressure higher than the reclining. At sixty seconds this majority was somewhat lessened. The lowest point in the blood pressure occurs about ten seconds after the change. If in the same individual pressures are obtained at seven

or eight seconds or about twelve seconds after the change, the drop is usually not as great as that obtaining at ten seconds. The diastolic pressure at the first reading showed a rise, as compared to the reclining diastolic pressure, in about 76 per cent of the individuals tested. The pressure fell in approximately 18 per cent and in 6 per cent it remained unchanged. These percentages did not change significantly after the first reading. In four individuals this procedure was repeated several times, in an effort to time the readings so as to have more points on the curve. When the curve is filled in (Fig. 2, light lines) it does not differ significantly from that obtained by joining the three points. In this chart the diastolic pressures are also shown.

Among those tested was one of the "ends" of the football team. These tests were run in the midst of the football season and might therefore be said to be on an individual in the best condition obtainable by training. His results showed the same reactions as those of an untrained individual.

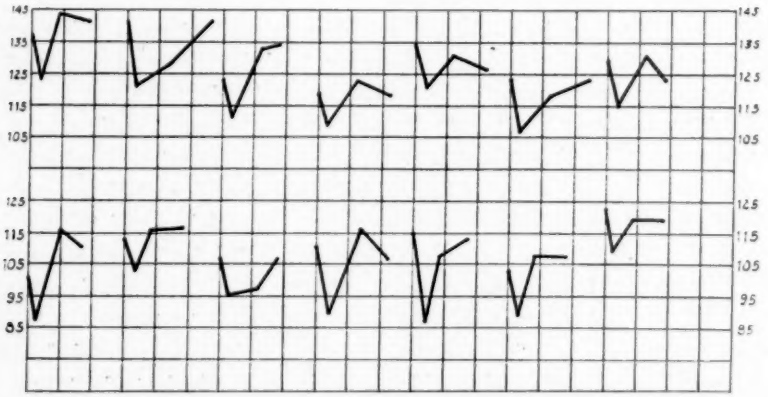

Fig. 1.—Systolic pressures on changing from recumbent to standing position. Fourteen adult males. Vertical lines represent thirty-second intervals; transverse lines, 10 mm. Hg pressure.

Among the students tried was one with a high reclining pressure (158 systolic). Although we tried three times we could never get a lower systolic pressure when he stood than the reclining value. We do not know if it is characteristic of people with high blood pressures to react in this manner. Hill mentions a monkey in which the same phenomenon occurred. We are also not sure about the accuracy of the sphygmomanometer at this level.

Thus we see that with a change in position from reclining to standing there is a sharp drop in systolic pressure along with a slight rise in diastolic pressure. Very quickly in most cases the systolic pressure recovers a large percentage of this drop, and in many instances exceeds the original reclining systolic value. For the majority of individuals this is complete within thirty seconds. At sixty seconds the height of systolic

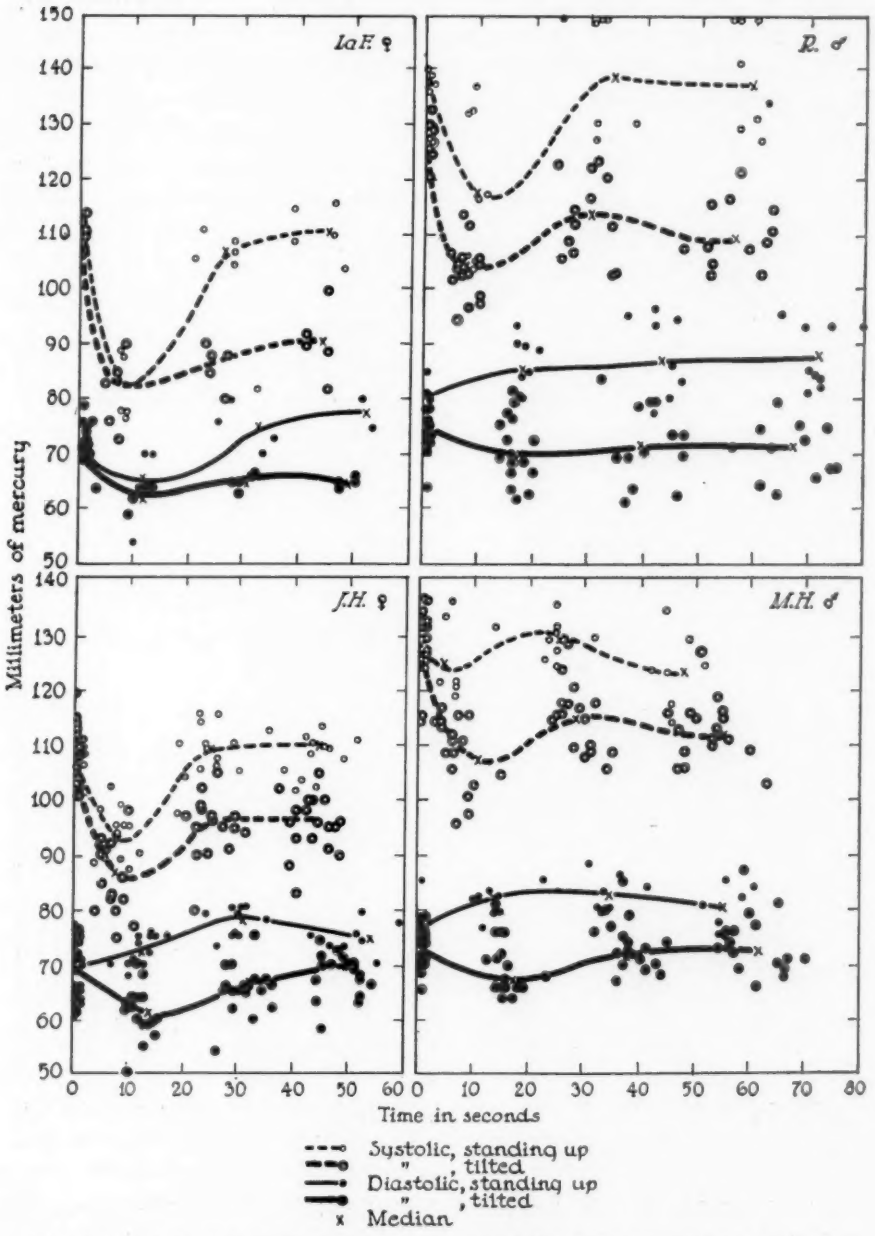

Fig. 2.—Systolic and diastolic pressures on changing from recumbent to standing (light lines) and tilting positions (heavy lines) repeated on 2 males and 2 females.

pressure is somewhat lessened. The sequence of events seems to be as follows: the change in position by a simple physical process due to the shifting of the blood into the abdominal cavity causes a sharp drop in systolic pressure. Very soon after this has happened the process of com-

pensation begins; reflexly, as will be shown later. This compensation, on the average, reaches its maximum effect within thirty seconds after the change in position, and at this point the indications are that a slight overcompensation exists, and that the normal level for standing is reached approximately after one minute.

When the Subjects Were Tilted.—Measurements were made in the same way upon the same group of subjects when they were tilted from

Fig. 3.—Systolic and diastolic pressure changes on tilting from recumbent to vertical position. Upper figures represent 8 different females and 8 different males. Lower figures represent repeated tilts on same subjects. Vertical lines represent fifteen-second intervals.

the horizontal to the vertical instead of standing. The subjects were so adjusted on the tilting board that the arm bag remained at the level of the heart. The results may be seen in Fig. 2 (heavy lines) and in Fig. 3. Fig. 2 represents the results of standing and tilting repeated on the same individuals a number of times, while Fig. 3 shows the result of tilting on 8 men and 8 women, and the results of tilting two individuals (a male and female) a number of times. In both charts systolic and diastolic pressures are shown. It will be noted that the systolic drop of

pressure is greater on tilting than on standing and that the amount of compensation which followed the initial drop is less. In no case was the systolic pressure at the end of thirty seconds higher than the reclining pressure, as was the case in standing. At the end of sixty seconds the systolic pressure was much less than the reclining level and the diastolic pressure was in most cases less than the reclining, while it was higher when the person stood up. The only explanation for the differences in the reaction to the change of position is that the differences were due to the muscular effort involved in standing up. When a person stands from the reclining position there occur strong contractions of abdominal muscles. This would increase intra-abdominal pressure, improve the venous return to the heart, and aid in the compensatory return of the blood pressure level. This factor is not present in tilting and probably accounts for the greater part of the difference in the response of these two methods of changing the position of the body from the horizontal to vertical.

The Effect of the Change in Position From Vertical to Horizontal by Tilting.—In order to determine the effect of a change in position from vertical to horizontal the subject was started in the horizontal position as in the previous experiments. He was then tilted into the vertical position and allowed to remain there until the blood pressure was stable over a three-minute period (no changes greater than three mm. Hg from minute to minute). After this point had been reached the subject was tilted back into the horizontal position and a series of blood pressure measurements were taken, three within the first sixty seconds, more or less, then one every minute until five minutes had elapsed. Usually by this time the values rather closely approximated the previous reclining record. This procedure was carried out on two subjects, seven times on one and four times on the other. The reaction of the two subjects, as may be seen from Fig. 4, differed somewhat. In one subject there was a very sharp rise of systolic pressure with the reverse tilt, to a level considerably higher than the original reclining level. The systolic pressure then gradually fell until finally after a few minutes it was approximately equal to the former reclining level. In this subject the diastolic pressure rose slightly and then fell to the former reclining level. As a result there was a rapid rise in pulse pressure to a level higher than the former reclining one, with a gradual decrease after this until the former reclining level was reached. On the other hand, the second subject, when tilted from the vertical to the horizontal position, showed a very sluggish rise in systolic pressure, and the reclining level was reached only after a minute had passed. At no time did the systolic pressure greatly exceed the former reclining level. However, with the shift in position there occurred a considerable drop in diastolic pressure, which after a period of time showed a tendency to recover toward the

former reclining level. This return was not completed within five minutes. However, the pulse pressure curve in this case was somewhat similar to that in the first case. Therefore, one might say that although the mechanism in these cases differed, the results upon the circulation,

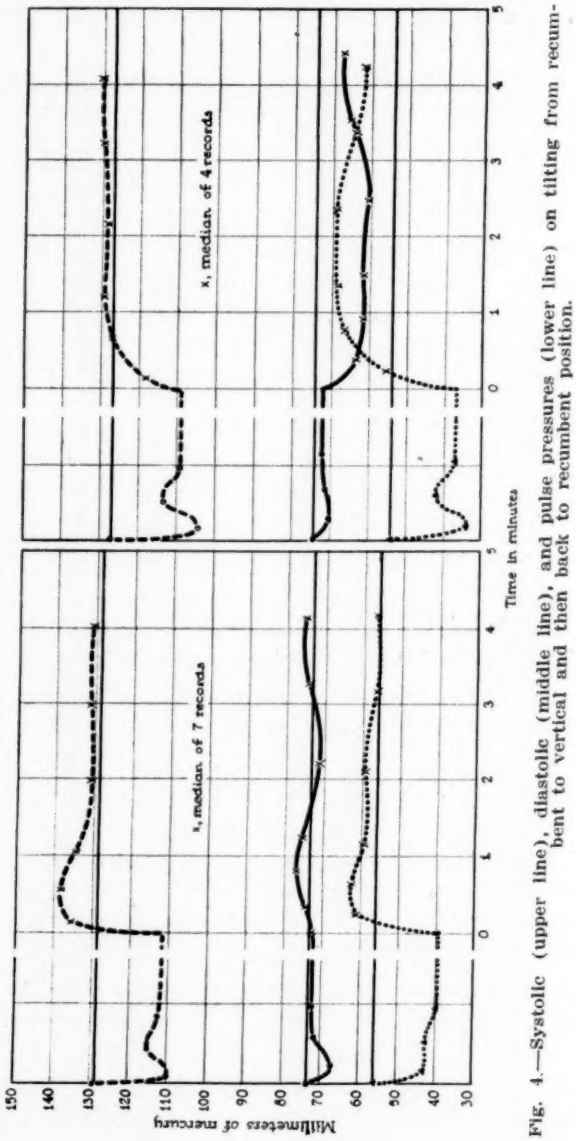

Fig. 4.—Systolic (upper line), diastolic (middle line), and pulse pressures (lower line) on tilting from recumbent to vertical and then back to recumbent position.

in terms of pulse pressure, were about the same. The curves bring out the point noted before, namely, that no two subjects react exactly alike.

2. The Course of the Blood Pressure

After the First Minute in Subjects Who Stood Up.—In a study of the effect of controlled exercise upon physical efficiency over 300 male, fresh-

man, students were given a modification of the Turner test.[3] The Turner test, which is a cardiovascular test of physical efficiency, is based upon the reactions of the blood pressure and pulse rate to the change in position from reclining to standing, and the effect of prolonged quiet standing upon blood pressure and pulse rate. In the modification of the test used here the blood pressure was measured first in the reclining position after the subject had been reclining for at least five minutes. Then the subject arose with as little effort as possible and a series of blood pressure records were made, one each minute for the first three minutes, then one every other minute until fifteen minutes had elapsed. Many of the subjects exhibited signs of excitement during the first trial. This shows up most in the heart rate. Although the blood pressure had ceased to fall after five minutes of reclining, the pulse rate on the first trial averaged 75 for all the subjects, 69 on the second trial, and 63 on the third trial. On trying a number of students a fourth and fifth time there was practically no change from the third trial. After one minute of standing the rates were 91, 88, and 84 for the three trials. The data presented on the pressure changes are from the third trial. One minute after the change in posture 31.6 per cent of this group of over 300 who took the test had a systolic blood pressure higher than the reclining level, 58.7 per cent had a systolic pressure lower than the reclining, and 9.7 per cent remained the same. In the case of the diastolic pressure 82.7 per cent were higher than the reclining level, 9.7 per cent were lower, and 7.6 per cent remained unchanged. In both systolic and diastolic pressures these percentages did not change significantly within the first three minutes, and the average level of blood pressure also did not change significantly within the first three minutes. Furthermore, the average blood pressure remained practically constant for the remainder of the fifteen-minute period. The greatest variation from average to average was less than ½ mm. Hg. These records indicate further that the compensatory changes of blood pressure to the change in posture from reclining to standing are completed within the first minute. Of course, in some individuals this may not be the case, but it certainly is for any large normal group as well as most normal individuals. The percentage of individuals having a higher systolic pressure on standing (31.6 per cent) is less than that found by most others. Schneider and Truesdell,[4] on 2,000 cases of students, found 55.5 per cent had a higher standing systolic pressure than recumbent and only 26.5 per cent a lower. We believe this is because there was probably less excitement connected with our tests and we may have had a better selected group. The figure given by Schneider and Truesdell (55.5 per cent higher systolic pressure) corresponds more to our unselected group described in the first part of this paper.

Prolonged quiet standing may be a severe strain on the circulatory system of many normal individuals since it is not extremely rare to find

seemingly normal individuals faint before fifteen minutes is over. Turner also observed this with some of her subjects. In the course of this experiment each subject was tested three times. Since there were approximately 300 subjects a total of 900 tests were made. During the course of these 900 tests, although we had a selected group, some 40 faintings were observed, about one in each 22 tests. However, 25 of these faintings occurred in the first trial, 10 in the second, and only 5 in the third. One subject fainted in all three trials, a few fainted in two trials but most fainted only once in the three trials. Fainting as a reaction to prolonged quiet standing in this test might be classified as a result of two primary causes. First, in the great majority of the subjects who faint in the first trial and then reacted normally in the

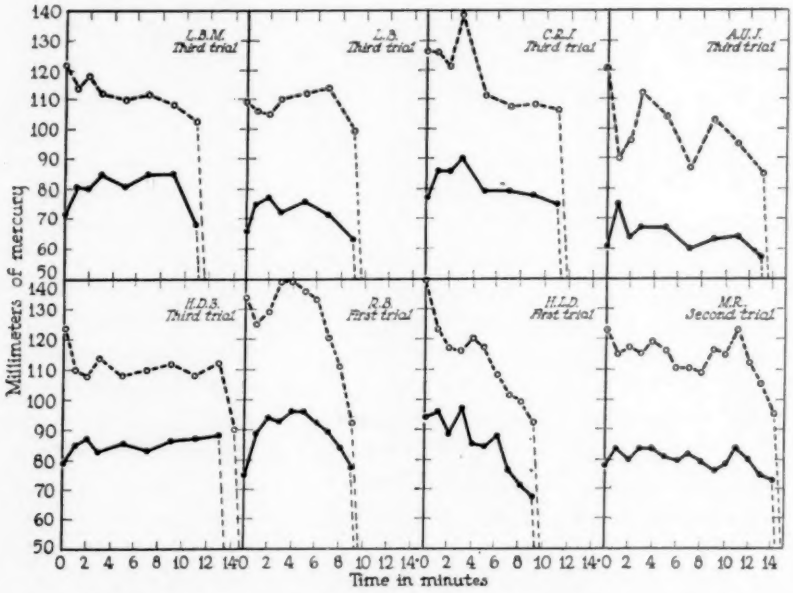

Fig. 5.—Systolic and diastolic pressure changes during quiet standing preceding fainting.

subsequent trials, the fainting undoubtedly had a psychogenic basis. In other words, the nervousness or apprehension of the subject who was unfamiliar with this type of examination affected directly or indirectly the cardiovascular reactions in such a manner as to produce a sudden drop in blood pressure. This resulted in fainting. When these subjects became familiar with the test, and the fear was lost, they reacted normally. The second primary cause of the fainting was an inadequate cardiovascular regulating mechanism. In these subjects the faints occurred more than once, or in the trials in which they did not faint they showed great instability in their reaction to change in posture and quiet standing. In these cases the fainting was undoubtedly due to the inability of the cardiovascular system to remain compensated during a

period of prolonged quiet standing. In most of the subjects who fainted the systolic pressure kept dropping for a number of minutes before the faint but in a few subjects the drop was very rapid as may be seen from the chart.

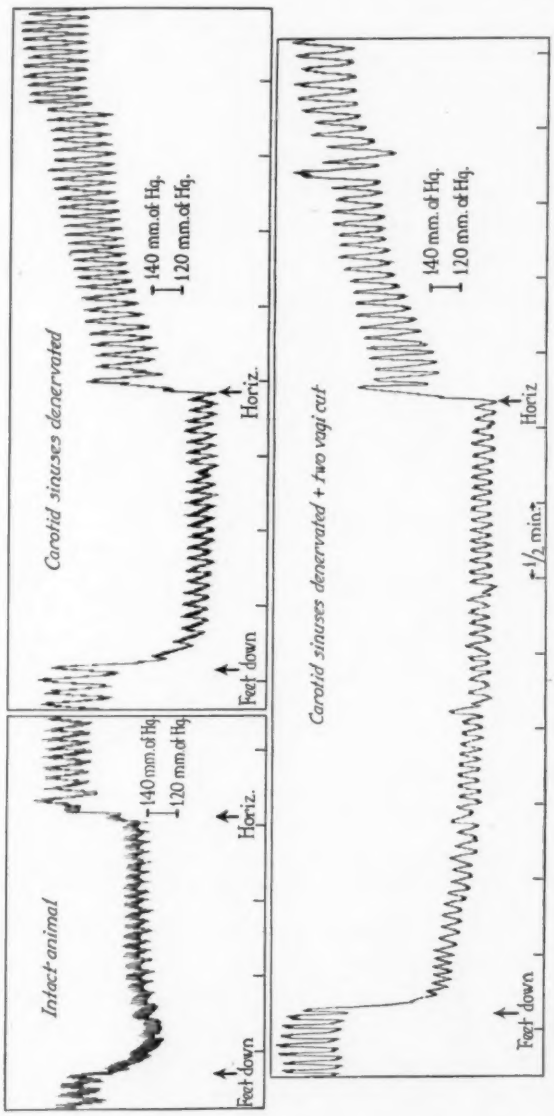

Fig. 6.—Blood pressure changes in dog (morphine-ether anesthesia) on turning from horizontal to feet-down position on (a) intact animal; (b) after denervation of carotid sinuses; (c) after denervation of carotid sinuses and section of both vagi.

3. Experiments on Animals

It seemed probable that reflexes are responsible for the readjustment in the pressure on standing and to test this matter experiments were made on dogs using Hill's technique.[1] Most dogs when they are tilted from the horizontal to feet-down position show the drop of pressure

with little or no tendency for the pressure to rise no matter how long the animal is kept in the vertical position, as can be seen in Fig. 6. Occasionally one finds a slight compensatory rise but we have never seen anything comparable to that found in man.

We tried animals under morphine-ether, sodium amytal, and after decerebration. However, that, even in the dog, reflexes are tending to keep up the pressure can be seen from the effects of denervating the carotid sinuses and section of the vagi. It will be noticed that the drops of pressure are greater and steeper than before and any slight tendency toward compensation is lost. Edholm and McDowall[5] state that denervation of the carotid sinuses makes no difference in the gravity effect. In our work on some 25 dogs the above mentioned differences have always been noted.

SUMMARY

On changing from the recumbent to standing position the systolic pressure is from 5 to 40 mm. Hg below the recumbent level about ten seconds after the change. There is a rapid recovery after this initial drop and after about thirty seconds many have regained or passed the recumbent level. In some few cases the recovery is slower. Diastolic pressure usually rises slightly on standing. The same type of reaction is seen when the subjects are tilted into the vertical posture but the drop is greater and the recovery less. Prolonged quiet standing is a severe strain on the circulation as shown by the frequency of fainting. Reflexes from the carotid sinuses and arch of aorta are responsible (in part at least) for the reactions leading to the recovery of the pressure.

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AN ANALYSIS OF THE DIAGNOSTIC CRITERIA OF ANGINA PECTORIS

A Critical Study of 100 Proved Cases*

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HEBERDEN'S classic description of angina pectoris[1] portrays the clinical characteristics so vividly that typical instances can be recognized without difficulty. Experience discloses, however, many variations of the clinical picture; furthermore, symptoms closely simulating angina occur in patients without heart disease. As a result, it is frequently difficult or even impossible to be certain of the diagnosis.

It is generally agreed that observation of the patient during an attack is a valuable aid in diagnosis. The majority of descriptions, including that of Heberden, are based not on actual observation, but on information obtained from patients suffering from the condition. The purpose of the present communication is to compare the patients' descriptions with observations made during actual attacks of angina pectoris in order to establish the criteria for diagnosis and to determine the frequency of atypical forms of the syndrome.

METHOD OF STUDY

During the past four years approximately two hundred patients suspected of having angina pectoris were referred for diagnosis and study from the out-patient department, the medical wards, and the private practice of local physicians. A detailed clinical history was obtained by at least two independent observers and a thorough physical examination with special reference to the heart was performed. A determination of the blood hemoglobin and blood Wassermann reaction was made in each instance, and further blood studies were performed when indicated. Electrocardiographic studies and measurements of the heart size from seven-foot roentgenograms were made in most instances. The basal metabolic rate[2] and the serum cholesterol[3] were measured in many of the patients.

The reaction of the patient to exercise was observed in every instance irrespective of the findings in the clinical history concerning the precipitation of attacks in daily life by exertion. Other means of inducing angina (adrenalin[4] or anoxemia[5]) were tried in several instances but were unsatisfactory. The exercise, carried out according to the

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method previously described,[6] consisted of repeatedly mounting and descending a two-step staircase in a room maintained between 45 and 55° F. The exercise continued until the patient either developed a typical attack of angina pectoris or became fatigued without experiencing other discomfort.

If the patient developed angina pectoris, various observations were made *during the attack.* The actual duration of the pain was measured by stop watch. The areas to which distress was referred were determined by pointing in rapid succession to various parts of the chest, back, arms, etc., and asking whether pain was felt at that moment in that region. The patient was requested to describe the character of the discomfort. Both during and after the attack an attempt was made to learn in what respects the induced attack resembled or differed from those experienced in daily life. The accuracy of the findings was tested by repeating all observations in almost every patient.

RESULTS

The studies outlined above were made in 207 patients. The symptoms of 54 patients were apparently due to disease of the lungs, cervical or thoracic spine, esophagus, diaphragm, stomach, or gallbladder (Cases 1 to 11). The remaining 153 patients had angina pectoris. In two of these the attacks were precipitated by episodes of paroxysmal rapid heart action, one had thyrotoxicosis, one had marked secondary anemia, two had rheumatic heart disease, and two had syphilitic aortitis. The remaining patients (145) had angina pectoris presumably due to coronary artery disease. For simplicity of analysis, 100 consecutive patients in whom we were able to obtain all or most of the desired special studies were selected from the latter group. These 100 patients differed in no way from the entire group of 145 except for completeness of data.

Sex, Age, Race, and Associated Diseases

There were 77 men and 23 women; the characteristics of the disease were identical in both sexes.

The duration of the disease up to the time of study varied from five weeks to fifteen years. At the time of onset of the symptoms 65 per cent of the patients were between fifty and sixty-nine years of age. Five patients (3 men and 2 women) were under forty years of age (Table I).

Nine of the patients were non-Jewish. Race made no evident difference in the characteristics of the disease.

Thirty-seven patients had one or more attacks of coronary thrombosis; seven suffered from intermittent claudication of the legs; five had diabetes.

History

Symptomatology.—One of the most characteristic features of the condition was the difficulty which patients experienced in describing the character of the discomfort. Questioning during an attack was frequently of distinct value. In all instances the sensation was described as disagreeable and uncomfortable, and in three-fourths of the patients as distinctly painful (Table II). The pain was obviously not as definite as that experienced in other conditions; in only six individuals was it sharp. Pressure or squeezing or their equivalents (heaviness, tightness) were frequent complaints, but patients agreed that these were inadequate descriptive terms.

TABLE I

THE AGE OF PATIENTS AT THE ONSET OF ANGINA PECTORIS

AGE (YEARS)	PER CENT OF PATIENTS
34-39	5
40-44	12
45-49	18
50-54	29
55-59	20
60-64	13
65-69	3

TABLE II

THE SYMPTOMATOLOGY OF ANGINA PECTORIS

SYMPTOM	PER CENT OF PATIENTS
Pain	76
Pressure (heaviness, weight)	52
Dyspnea	48
Squeezing (tightness)	33
Choking	19
Palpitation	11
Belching	10
Burning	4

Respiratory Symptoms: Approximately half of our patients found it "hard to breathe" during attacks. Exactly what was meant by this expression was not always clear; in some instances it was apparently hyperpnea while in others it was a sensation of stifling. Patients who complained of shortness of breath usually showed an increased depth and rate of respiration during attacks induced by exertion, but similar respiratory symptoms were present when the attacks occurred at rest or were induced by excitement. Thirteen patients who denied shortness of breath showed definite and striking hyperpnea when observed during paroxysms.

Palpitation occurred in eleven patients. The occurrence of this symptom frequently made it difficult to determine whether the discomfort was characteristic of angina or was simply consciousness of the heart-

beat. Close questioning revealed that patients with angina pectoris experienced pain, pressure, or squeezing in addition to palpitation. Observation showed that the pain disappeared before the consciousness of the heart action subsided. The palpitation in this group was not associated with any abnormal rhythm and frequently continued after the heart rate had returned to normal.

Belching occurred in ten patients. In several instances termination of the attack and belching were almost simultaneous; in others belching occurred only while the patient was experiencing pain. Patients stated that, in association with the pain or squeezing, they experienced the sensation of a lump or a heaviness under the sternum which they felt would disappear on bringing up gas. It was obvious from observation that the belching followed the swallowing of air.

Fear of impending death was an infrequent and inconstant symptom. It was particularly experienced by hypersensitive, anxious patients, especially during the first few weeks or months after the onset or following an increase of symptoms. It frequently disappeared after a few attacks induced in the presence of a physician.

The Onset of Attacks.—In every instance the onset was sudden and required only a few seconds to reach its maximum intensity. The attacks usually came without warning, but occasional patients stated that unusual exertion or emotion might be attended by a premonition that an attack was about to develop.

The Effect of Cold.—Fifty per cent of eighty patients, who had observed the effect of temperature, noted that attacks were induced more readily by walking in the cold or against the wind. Five per cent developed pains more readily in warm weather. The remaining 45 per cent felt that temperature made little difference in the frequency of attacks. Direct observation has shown that the temperature of the environment is a very important factor in the ease of inducing attacks.[6]

The Effect of Food.—We have not yet encountered patients who develop angina *solely* as a result of overeating. The usual story is that after heavy meals an attack is likely to be induced by less exertion than at other times (Table III). This has been demonstrated by actual

TABLE III

CONDITIONS UNDER WHICH ATTACKS OF ANGINA WERE PRECIPITATED

CONDITION	PER CENT OF PATIENTS
Exertion	100
Emotion	65
After meals	28
At rest	30
During sleep	24

observation.[6] One patient regularly developed tachycardia and angina following coffee; this was probably a response to caffeine.

The precipitation of the attack by exertion was an important diagnostic point (Table III). Two patients stated that attacks came only at rest and not on exertion; ten stated that attacks were usually induced by emotion but at times, or in the past, were precipitated by walking or climbing stairs. It was obvious from the clinical histories of these individuals that they rarely undertook any great degree of exertion. Regardless of the clinical history, *all* patients developed typical anginal attacks on exercise in the cold room except two individuals who had pain only in association with attacks of paroxysmal rapid heart action and one who had thyrotoxicosis.

The Duration of Attacks.—It was obvious that patients were unable to estimate accurately the duration of these paroxysms of discomfort. Half of the patients stated that the pain lasted either a few minutes or from five to ten minutes.[7] It is important to note that only four patients estimated that their attacks were *usually* fifteen minutes or longer in duration. Actual measurement of the duration of attacks indicated that they were practically always less than three minutes in duration.[7]

Effect of Nitroglycerin in Terminating Attacks: Eighty-two patients had tried this therapy. Forty-eight per cent believed that placing the tablet under the tongue shortened the attacks, 23 per cent were certain that it had been of no benefit; the remaining 29 per cent could not be certain whether or not it had made any difference. Patients without angina pectoris frequently reported relief from pain definitely noncardiac in origin by using nitroglycerin (Case 9). Actual observation often failed to substantiate the patient's impression of the effect of nitroglycerin on the duration of attack.[7]

Localization and Radiation of the Discomfort.—There was considerable difficulty in describing the distribution of the discomfort unless patients were questioned while actually experiencing pain. So far as

TABLE IV

LOCATION AND RADIATION OF DISCOMFORT DURING ANGINAL ATTACKS*

LOCATION	ONSET OF ATTACK PER CENT OF PATIENTS		SUBSEQUENT INVOLVEMENT PER CENT OF PATIENTS		TOTAL PER CENT OF PATIENTS
Substernal	74		9		83
Left chest (anterior)	21		13		34
Apex of heart		6		2	
Axilla		0		3	
Shoulder (anteriorly)		0		2	
Right chest	11		2		13
Left arm	8		22		30
Right arm	1		9		10
Thoracic spine	16		5		21
Epigastrium	6		2		8
Throat	2		7		9
Neck	1		8		9
Left side of head	0		1		1

*In many patients pain occurred in several different areas simultaneously.

the patients could determine, identical areas were usually involved during the induced attacks and in those experienced in daily life; any slight difference was evident by comparison. Observation during attacks showed that all patients experienced discomfort in the anterior chest (Table IV). This roughly included an area between the anterior axillary lines, the lower costal border including the epigastrium, and the level of the first interspace including the suprasternal notch.

The Distribution of Pain at the Onset of the Attack.—In 89 per cent of the cases the discomfort began somewhere in the region outlined above. The substernal area (including about one inch to either side of the sternum) was by far the most common region to which the pain was referred; nevertheless, in one-fourth of the patients there was no substernal discomfort. The left chest was involved twice as often as the right. In six patients the pain began over the apex of the heart; in each of these instances the pain later radiated elsewhere in the anterior chest or the left arm. In eleven individuals the pain did not begin in the anterior chest; in three of these, the thoracic spine was the site of onset; in three, the epigastrium; in three, the left arm; in one, the right arm and in one the left lower jaw.

Pain in the shoulder proved to be either the anterior axillary fold or the region over the head of the humerus. Many patients experienced pain in the middle or upper thoracic spine, but this was rarely a prominent complaint and was elicited only by careful questioning during an attack. Only one patient had pain in the region of the scapula (left). With the exception of this patient and those who had pain in the spine, the posterior and lateral aspects of the thorax were free of discomfort.

Radiation of the Discomfort.—The description of the radiation of the discomfort often helped to clarify the diagnosis. The left arm and the left chest were the regions to which the pain radiated most frequently. It was often difficult for the patient to remember whether the inner or the outer aspect of the arm was affected but observation revealed that in every instance the inner aspect of the arm, i.e., the region of the biceps, the antecubital fossa, and the ulnar surface of the forearm, was involved. Two patients had pain along both the inner and outer surfaces of the arm.

In 56 per cent of the patients there was no radiation of the pain.

The Frequency of Attacks.—The majority of patients had one or more attacks each day, approximately 10 per cent had one attack or less each week (Table V). The frequency of attacks was of no value in diagnosis.

Physical Examination.—Physical examination was of little value in establishing the diagnosis of angina pectoris. The physical build of the patient was of some interest: sixty-one were stocky; thirteen were obese; the remaining twenty-six were definitely thin.

During attacks patients frequently developed an anxious expression and at times held both hands to the chest or clenched their fists as if to show that the sensation was one of squeezing or crushing. In some instances this aided in diagnosis. After the first or second induced attack, however, such patients usually lost their anxious expression and apparently were not uncomfortable.

The Electrocardiogram, Blood Pressure, and Heart Size.—It is evident that typical angina pectoris frequently occurs in patients with no abnormalities in heart size, blood pressure or electrocardiographic tracings (Table VI). One-half of the patients showed an entirely normal electrocardiographic tracing, the other half showed changes consistent with

TABLE V

FREQUENCY OF ATTACKS IN 81 PATIENTS

	PER CENT OF PATIENTS
About one a month	7
About one a week	5
2 to 6 a week	31
1 to 2 a day	28
2 to 5 a day	24
5 or more daily	5

TABLE VI

THE ELECTROCARDIOGRAM, BLOOD PRESSURE, AND HEART SIZE IN ANGINA PECTORIS

	PER CENT OF PATIENTS
Electrocardiographic evidence of coronary artery disease*	50
Hypertension	44
Cardiac enlargement (x-ray)†	25
Normal blood pressure, electrocardiogram, and heart size‡	26

*Studies made on 97 patients.
†Studies made on 74 patients.
‡Studies made on 70 patients.

coronary artery disease (slurring, spreading, or notching of the QRS complexes, elevation or depression of the S-T segment, inversion of T_1 or T_2, upright T_4 or absent Q_4). One patient had auricular fibrillation without decompensation. It must be remembered that similar electrocardiographic changes are seen in patients without angina pectoris.[12]

The blood pressure was measured in the right arm with the patient in the sitting position and was determined only once or twice on any given day. A more careful study with repeated measurements would undoubtedly yield a higher percentage of low blood pressure values. Hypertension (greater than 159 mm. Hg systolic or 99 mm. Hg diastolic) was found in slightly less than one-half the patients. Systolic pressures greater than 200 were rare. There was little demonstrable difference between the blood pressure readings of men and women. Two women with angina pectoris, each thirty-eight years of age, had blood pressures

of 112/58 and 112/80; in neither patient was there any evidence of preexisting hypertension or coronary thrombosis.

Only one-fourth of the patients showed cardiac enlargement by x-ray examination.

Twenty-six per cent of all patients showed no abnormality in the electrocardiogram, blood pressure, or heart size by x-ray examination.

The Basal Metabolic Rate and Serum Cholesterol Values.—It has been suggested that low basal metabolic rates are relatively common in patients with angina pectoris,[10] but few figures are available. The basal metabolism of 40 per cent of our patients was between –11 and –25 per cent (Table VII). In no instance was there any clinical evidence of myxedema.

TABLE VII

THE BASAL METABOLIC RATE IN ANGINA PECTORIS (74 PATIENTS)

BASAL METABOLIC RATE	PER CENT OF PATIENTS
+11	4
± 0 to +10	24
± 0 to -10	32
-11 to -15	18
-16 to -25	22

TABLE VIII

SERUM CHOLESTEROL VALUES IN ANGINA PECTORIS (68 PATIENTS)

SERUM CHOLESTEROL MG. PER 100 C.C.	PER CENT OF PATIENTS
150-199	10
200-249	31
250-299	43
300-349	10
350-399	4
400-413	2

Approximately 60 per cent had an increased cholesterol content of the blood (Table VIII). In general, a low basal metabolic rate was accompanied by an elevation of the serum cholesterol, but high cholesterol values were also found in individuals with normal metabolic rates.

Angina Pectoris Associated With Other Forms of Heart Disease, Anemia, or Thyrotoxicosis.—The character, the location, and the radiation of the discomfort were the same in all cases of angina pectoris regardless of whether the underlying pathology was coronary arteriosclerosis or some other condition which might induce myocardial anoxemia. In patients with other forms of heart disease, however, attacks were frequently more severe, longer in duration, and more likely to come on at rest or during sleep than in uncomplicated Heberden's angina.

We were unable to induce attacks by exercise in two patients whose attacks occurred only during episodes of paroxysmal rapid heart action (auricular fibrillation or auricular tachycardia). These patients stated

that the palpitation usually came while at rest and the pain began shortly after the onset of the rapid heart action and disappeared shortly after the cessation of the arrhythmia.

Attacks indistinguishable from uncomplicated Heberden's angina were induced in two patients with rheumatic and two with syphilitic aortic disease. Four other patients with aortic disease were not included in the present series of 207, for it was considered inadvisable to have them exercise. The clinical histories of two with aortic stenosis (one of rheumatic, the other apparently of arteriosclerotic origin) differed in no way from the 100 analyzed above. The other two had aortic regurgitation of rheumatic origin. Attacks of angina were ushered in by an increase in heart rate and systolic blood pressure while at rest, on motion in bed, or during meals. The characteristics of these attacks were similar to those secondary to paroxysms of abnormal rhythm.

One patient with anemia differed in no way from the hundred cases analyzed above. Correction of the anemia resulted in an increase in the amount of work which could be done before developing angina but did not entirely prevent attacks. One patient with thyrotoxicosis has been reported previously.[6] We were unable to induce attacks of angina in this patient by exertion; thyroidectomy has resulted in improvement but not "cure" of the angina.

COMMENT

The majority of patients with Heberden's angina are persons of stocky or "vascular" build; men are more commonly affected than women; the ages forty-five to sixty-five years are most frequent and from one- to two-thirds of patients show abnormalities in the electrocardiogram, blood pressure, heart size, basal metabolic rate or serum cholesterol level. The clinical history may reveal that the attacks are associated with a fear of impending death or that the pain can be terminated by nitroglycerin. In individual instances, however, these findings are of no specific diagnostic value.

The first and most important step in diagnosis is to obtain an adequate description of the symptomatology. In our experience all patients with angina pectoris showed five diagnostic characteristics in common:

1. *Onset* sudden, in "attacks."
2. *Duration* short, usually more than a few seconds but less than "fifteen minutes."
3. *Symptoms* difficult to describe; pain, pressure, squeezing, choking, or their equivalents.
4. *Region involved,* the anterior chest (including the epigastrium) and the inner aspect of the arms (especially the left). Radiation of the discomfort is important, if it occurs.
5. *Attacks precipitated by exertion,* especially climbing stairs or walking in the cold.

Patients who lacked one or more of these five features proved to have either noncardiac disease as the cause of their symptoms or angina pectoris plus some complicating disease.

The history as volunteered by the patient must be analyzed and evaluated to determine its reliability, accuracy, and completeness. Additional questioning is frequently necessary to obtain adequate information concerning the five diagnostic points. Certain variations are frequently met and deserve comment; in most instances the disagreement is apparent rather than actual.

Onset and Duration.—An occasional patient has prolonged attacks or constant pain. Such individuals, however, may recognize episodes of sudden exacerbation of symptoms which have all the characteristics of anginal attacks. The constant pain in such instances is frequently a comparatively mild soreness or hyperesthesia of the skin or bone which persists for hours or days after the acute paroxysm has subsided.

An *occasional* attack of long duration does not rule out angina pectoris; in fact many patients pass through a period of comparatively prolonged and more severe attacks.[9] The significance of these is not clear. In some instances careful study may prove the episode to be due to coronary thrombosis; in other instances fever, leucocytosis, and electrocardiographic changes may be absent, but an elevation in sedimentation rate may occur, suggesting myocardial damage.[8] Patients whose attacks always last longer than one-half hour usually prove to have no cardiac disease as the cause of the prolonged attacks (Cases 6 and 10).

The characterization of the discomfort will vary with the experience and vocabulary of the patient. An owner of real estate described "the Empire State Building pressing" on his chest; a retired cowboy felt "a lariat about the throat." The one characteristic in common is a vague unrest or distress difficult to describe.

The region affected is best determined by having the patient point specifically to the area where he experiences pain during attacks. This may be difficult and observation during attacks may reveal an entirely different area of involvement. Discomfort experienced in the posterior or lateral aspects of the thorax (except the region of the dorsal spine), the outer aspects of the arms or the shoulders, or the abdomen should make one suspicious and search for a noncardiac explanation of all or part of the picture (Cases 8 to 11).

Precipitation of Attacks by Exertion.—The occurrence of attacks during rest or sleep and the effect of emotion is well known. In an occasional patient these aspects may be so prominent that the precipitation by exertion may be overlooked. Patients whose attacks *never* come on exertion are rare and are usually those who take but little exercise. Such patients may have had attacks on effort in the past; in many instances this association of pain and exertion has been the cause of the

limitation of activity. It is frequently helpful to ask such patients what would happen if they were to run up stairs.

The apparent variation in the amount of work which patients can perform from day to day before developing pain argues against exertion as an important factor. These variations, however, are due to changes in the temperature of the environment; the emotional state of the individual; the amount of food recently eaten; physiological changes occurring after attacks which make successive paroxysms either more or less easily precipitated; and, at times, to actual variations in the course of the disease. When patients exercise under standardized conditions, the amount of work which can be done before inducing an attack is extraordinarily constant.[6]

The terms "angina of effort," "angina of rest," and "angina of emotion" are probably misnomers. So far as can be determined, these are simply different conditions under which the same symptom-complexes may be precipitated. It is more logical and satisfactory to speak of "angina *on* exertion," "angina *on* emotion," and "angina *during* rest or *during* sleep."

Angina pectoris secondary to valvular heart disease, aortitis, paroxysmal arrhythmias, anemia, or thyrotoxicosis was quite similar to that due to coronary artery disease, but the attacks were likely to be more prolonged and frequently occurred without obvious precipitating cause. The frequency of patients with such complicating features varies in different parts of the world. It is apparent, however, that they constitute a comparatively small proportion of the large group of patients who suffer from angina pectoris and that they rarely offer any great problem in diagnosis.

Difficulties in diagnosis are usually due to one of four reasons: first, the symptoms may suggest a noncardiac disorder. This is especially true if the discomfort begins in an unusual area, such as the epigastrium, arms, or jaw, or if other symptoms, such as belching, apparent relief by soda, or attacks following meals are a prominent part of the picture (Cases 1 to 4). Second, noncardiac disease may suggest angina. It must be remembered that precordial distress may be caused by pathological processes in the cervical or thoracic spine, lungs, diaphragm, esophagus, stomach or gallbladder (Cases 5 to 9). Third, the patient may have angina pectoris in addition to noncardiac disease. Under such conditions the anginal distress may be hopelessly interwoven with other complaints, making it impossible for even the most experienced examiner to be certain in his appraisal of the situation (Cases 10 and 11). Fourth, in many instances language difficulty, emotional instability, inadequate observation, or the vagueness of symptoms makes it impossible for the patient to present a clear picture of his sensations.

The standardized exercise tolerance test enables one to obtain specific information concerning four of the five important diagnostic points: the

ability to induce paroxysms by exertion, the speed of onset of attacks, the duration of symptoms, and the location of the discomfort. Additional information concerning the character of the discomfort can also be obtained at times by questioning the patient during an attack. In our experience, observation of the response to exertion has resulted in a change in diagnosis and treatment in many instances while in others important information not available from the clinical history was obtained.

The test is not infallible, but its accuracy is apparently great. Out of 207 patients tested, we have had reason to doubt the result in but six. Two patients who failed to develop discomfort on exertion suffered coronary thrombosis several months after being tested. The clinical histories did not warrant a definite diagnosis of angina pectoris in these individuals, but it is possible that they did have angina and were tested during a remission. One patient who developed pain on exertion died of carcinoma of the esophagus; no autopsy was performed, but it was felt that this patient had coronary arteriosclerosis. The two patients with angina secondary to paroxysmal rapid heart action and the one with thyrotoxicosis have been commented on.

It is neither necessary nor advisable to resort to an exercise or work test in every instance. Many patients are capable of describing their symptoms in a manner which leaves little to be desired, while adroit questioning of others will yield sufficient information concerning the important diagnostic criteria. We must never lose sight of the fact that angina pectoris is a serious condition, and coronary thrombosis or sudden death may come without warning. While it would appear that little danger is involved in a patient's undertaking, in the presence of a physician, exertion similar to that which he performs frequently in daily life, nevertheless, one should refrain from exercising patients whose symptoms are unusually severe, or those who experience "weakness" on exertion.

It is to be expected that errors will occur when the diagnosis rests solely on the patient's ability to describe his symptoms. The frequency of error decreases, however, as the examiner becomes more experienced and as attention is paid not only to the story as volunteered by the patient but also to the important diagnostic criteria above enumerated. There will remain, undoubtedly, a group of patients in whom it is impossible to be certain of the diagnosis from the history alone; the diagnosis in such patients can usually be made by observation during attacks, if necessary, precipitated by exertion.

SUMMARY AND CONCLUSIONS

1. Approximately two hundred patients suspected of suffering from angina pectoris have been studied in order to establish the criteria for diagnosis and to determine the frequency of atypical forms of the syn-

drome. The studies include a careful evaluation of the clinical history, physical examination, electrocardiographic tracings, teleroentgenograms of the heart, the basal metabolic rate, the blood serum cholesterol, and the patient's reaction to exercise under standardized conditions.

2. Five characteristics were of importance in the diagnosis of angina pectoris: the attacks were sudden in onset, short in duration, involved the anterior chest (including the epigastrium) and inner aspect of the arms, were induced by exertion in the cold, and consisted of a vague sensation of unrest or distress difficult to describe. Patients who lacked one or more of these features proved to have either no cardiac disorder as the cause of their symptoms or to have angina pectoris plus some complicating disease.

3. There were other characteristics which were encountered frequently but which were of no specific diagnostic value in any individual instance. These included abnormalities in the electrocardiogram, blood pressure, heart size, basal metabolic rate, serum cholesterol level, and the relief by nitroglycerin. Twenty-six per cent of all patients with angina showed no abnormalities in the electrocardiogram, blood pressure, or heart size by x-ray examination.

4. Angina pectoris due to valvular heart disease, paroxysmal rapid heart action, anemia, or thyrotoxicosis was quite similar to that secondary to coronary artery disease, but the attacks were likely to be prolonged and frequently occurred without obvious precipitating cause.

5. Difficulties in diagnosis were usually due to noncardiac disease simulating angina pectoris, angina pectoris simulating noncardiac disease, angina pectoris and noncardiac disease occurring together in the same individual, or inability of the patient to present a clear picture of his sensations.

6. Observation of the patient's reaction to exercise was frequently of distinct value in establishing the diagnosis or obtaining a more exact picture of the symptoms than was possible from the clinical history alone.

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CASE REPORTS

CASE 1.—*Angina Pectoris Simulating Gastrointestinal Disease.*

Mr. M. S., an instrument worker, had been in good health until the age of forty-two years, when he first noticed "a dull cramp" in the region of the epigastrium, which came on exertion, such as swimming. This lasted only a "few moments" and disappeared on rest. X-ray films of the gastrointestinal tract revealed no pathology. A diagnosis of "nervous indigestion" was made.

Two and one-half years later the patient noted that in addition to the epigastric discomfort there was a sense of choking and pain in the suprasternal notch, which, at times, radiated to the left arm. The attacks were only a few minutes in duration and disappeared on rest. A diagnosis of angina pectoris was made, and medical therapy was instituted but without improvement. A year and one-half later he was referred to the Beth Israel Hospital for total thyroidectomy.

Physical examination revealed no abnormalities. The patient was well nourished, short and stocky. The heart was of normal size by x-ray examination; blood pressure, 145/85; electrocardiogram showed left axis deviation, inverted T_2 and T_3. Basal metabolic rate was –8 per cent. Exercise in the cold room precipitated, after fifty-eight trips, an attack which was similar in all respects to those which he had had on the outside and was undoubtedly angina pectoris.

Comment.—Pain limited to the epigastrium suggested that this patient's symptomatology was due to a gastrointestinal disorder and only when discomfort radiated to the suprasternal notch and the left arm was it possible to make a definite diagnosis of angina pectoris. The precipitation of epigastric discomfort *by exercise*, the short duration of the symptoms, the relief by rest, and the lack of relationship to food, should have raised the suspicion that the condition might be cardiac rather than gastric.

CASE 2.—*Angina Pectoris Simulating Gastrointestinal Disease.*

Mr. P. S., aged forty years, a dry goods salesman, stated that three weeks before entering the hospital, while walking to work in the morning, he suddenly experienced pressure under the sternum which forced him to stop in order to catch his breath. There was no radiation of the pain, but it was accompanied by a feeling of choking and an intense desire to belch. The attack lasted about "two minutes" and left him feeling quite well. Since that time he had had five to six similar attacks, usually occurring while walking to work in the morning. On one occasion he took a Seidlitz powder with prompt relief.

Physical examination was essentially negative except for tenderness to palpation over the right costal margin. The blood pressure was 130/92. X-ray examination revealed no cardiac enlargement. Electrocardiographic tracings were normal except for prominent Q_2 and Q_3. Oral cholecystogram revealed normal filling and emptying. Blood serum cholesterol was 298 mg. per 100 c.c. Basal metabolic rate was –10 per cent.

Comment.—The history in this case is apparently quite similar to that of Case No. 5. Both patients were forty years of age. The attacks

had been noticed for only a few weeks. The discomfort in both instances was in the substernal region, was associated by a desire to belch, and was relieved by Seidlitz powder or bicarbonate of soda. Careful questioning, however, revealed important differences in the duration of the attacks and the relationship to food and exertion. The relief by seidlitz powder, in this case, was not real, for the attacks continued for several minutes after taking the powder, whereas other attacks not so treated were no more prolonged. After twenty-two trips in the cold room the patient developed an attack of angina pectoris which was typical of the attacks that he experienced on the outside. A month after discharge, the patient developed a coronary occlusion, from which he recovered.

CASE 3.—*Angina Pectoris Simulating Neuritis.*

Mrs. R. K., a housewife, was well until the age of forty-five years. At this time a panhysterectomy was performed, following which she developed vague aches and pains in various parts of her body. Her blood was found to show a slight increase in the number of white cells and the smear contained 50 per cent lymphocytes, all of which were normal. There was no glandular enlargement and no evidence of blood disease. Two years later she developed attacks of pain beginning in the left wrist and radiating up the left arm to the substernal region and to the apex of the heart. These were usually precipitated by exertion especially in the cold; excitement also induced attacks, and occasionally they awakened her at night. The pain she stated was of "a pressing, squeezing character as if the sleeve had become too tight." She was unable to tell whether the sensation was on the inner or outer aspect of her arm. With the pain she felt very short of breath. The attacks came on once or twice a week, and were frequently accompanied by belching.

Physical examination was entirely negative. The heart was not found enlarged by x-ray; blood pressure was 160/90. Electrocardiogram was normal except for left axis deviation. Basal metabolism was +3 per cent. Serum cholesterol was 269 mg. per 100 c.c.

Comment.—The patient believed she was suffering from indigestion, for belching accompanied the attacks. The pain in the arm, however, led to a diagnosis of neuritis, and she was treated accordingly for several months. Exercise in the cold room induced a typical attack of angina pectoris which began after 32 to 38 trips. The pain began on the flexor surface of the wrist, radiated up the inner aspect of the arm, and finally reached the midsternal region. The attack lasted one and one-half minutes and subsided first in the chest, then in the arm and finally in the wrist. For a period of approximately a year this patient was treated with various forms of medicinal therapy without any striking improvement. She died suddenly during sleep.

CASE 4.—*Angina Pectoris Simulating Dental Pathology.*

Mr. H. C., aged fifty-two years, a retired tailor, had been well, except for mild diabetes, until about two months before admission, when he began to complain of discomfort in the left lower jaw severe enough to force him to stop walking. This pain usually began as pain in the region of a capped tooth. If he persisted in walking, he felt a choking sensation in the throat, a squeezing sensation in the retrosternal region, and pain along the inner aspects of both arms. With the attacks he frequently broke out into a sweat. The paroxysms usually lasted "10 to 15 minutes."

Physical examination revealed a short obese individual in whom the left lower canine tooth served as one anchor for a bridge, and the cap had worn away at the base exposing the tooth. The blood pressure was 140/70. X-ray film of the heart showed slight enlargement to the left. Electrocardiogram showed low T-waves in all leads, inverted T_3, absent Q_4, M-shaped QRS_4. The urine showed no sugar; blood sugar was 123 mg. per 100 c.c. The basal metabolism was -19 per cent.

Ten months after the onset of symptoms, a denervation of the thyroid, according to the method of Lyon and Horgan,[13] was performed; this was followed by relief of pain in the chest and the right arm. He continues to have pain in the jaw and left arm on exertion and excitement.

Comment.—The patient was quite certain that the pain was due to his teeth. X-ray films revealed alveolar recession but no other pathology. It was inconceivable that dental pain should be induced by exertion and should spread to the neck, the chest, and the arms. Exercise in the cold room precipitated an attack after ten trips which was similar to that described by the patient. About two months later the duration and frequency of the attacks increased. The electrocardiogram at that time showed inversion of T_2 and T_3.

CASE 5.—*Gastrointestinal Disease Simulating Angina Pectoris.*

Mr. M. G. (35476A), aged forty years, complained of a sense of "pressure or heaviness" under the sternum, which came on while walking and after meals, did not radiate, and was occasionally relieved by belching.

Physical examination was essentially negative except for a blood pressure of 165/100, palpable and thickened brachial and radial vessels, the dorsalis pedis pulsation was absent.

Comment.—Angina pectoris was suspected, and the response to exertion was studied. No attack was precipitated by one hundred trips under the standardized conditions of the test. Further questioning revealed that the discomfort usually came on after his noonday meal, at which time he usually walked about the streets during his lunch hour; the symptoms also occurred after other meals, while at rest. The distress usually continued for approximately a half hour, was not aggravated by continued walking. Nitroglycerin gave no relief, but sodium bicarbonate gave immediate relief. It was obvious that this was not a case of angina pectoris but was more likely due to disturbed function of the gastrointestinal tract. The discomfort disappeared on a gastric regime.

CASE 6.—*Gallbladder Disease Simulating Angina Pectoris.*

Mr. J. S. had been previously examined in two other hospitals where diagnoses of arteriosclerotic heart disease, coronary thrombosis (old), and angina pectoris had been made. For three years before admission to the Beth Israel Hospital he had experienced attacks of severe, squeezing pain in the chest coming on once or twice a day, usually while resting quietly, frequently following meals. They were rarely induced by exertion, but the patient had been living a very inactive life. These attacks usually lasted from fifteen minutes to one or two hours, were unrelieved by nitroglycerin, and often required morphine for relief. On at least two occasions the attacks had been so severe that several weeks' rest in bed had been prescribed.

Physical examination revealed a hyperactive, short, stocky man. The left pupil was irregular and smaller than the right. There was peripheral arteriosclerosis. The blood pressure was 170/90.

Examination of the urine and blood revealed no abnormal findings. The blood Wassermann reaction was negative. Serum cholesterol was 280. Basal metabolic rate -2 per cent. The heart was not enlarged by roentgenogram; electrocardiographic tracings showed left axis deviation and a deep S_2. During the patient's stay in the hospital the symptoms disappeared entirely, and, after three weeks, he was discharged with diagnoses of hypertensive and arteriosclerotic heart disease, angina pectoris, pulmonary emphysema.

Six weeks later he returned with a story that ten days before reentry, while sitting quietly in a chair, he experienced an attack of squeezing in the midsternal region which lasted for two hours and required hypodermic medication for relief. This pain was preceded by profuse sweating. During the next few days he had several similar but less prolonged attacks. Examination at this time revealed essentially the same findings as at the previous admission. Repeat electrocardiographic tracings showed an inverted T_2, which later became upright.

Comment.—The history in this patient was consistent with angina pectoris. Certain features, such as the prolonged duration of the attacks and the onset during rest and following meals rather than on exertion, made it advisable to investigate further. X-ray films of the gastrointestinal tract revealed no pathology. Cholecystograms by both the oral and intravenous method revealed no gallbladder shadow. A roentgenogram of the cervical spine showed hypertrophic changes at the anterior and posterior margins of the cervical vertebrae.

Because of the apparent severity of symptoms the patient's response to exercise was studied with great caution. The first test was stopped after he did a relatively small amount of work (ten trips), and on each subsequent test the amount of work which he was allowed to do was increased. On the fourth test he made sixty-two trips in three and one-half minutes. This resulted in moderate dyspnea and fatigue of the legs but no precordial distress.

If this patient suffered from angina pectoris in as severe a form as was apparent from the history, it would have been impossible for him to have done this amount of work. Accordingly, he was discharged with instructions to take a low-fat, high carbohydrate diet, small meals, and tincture of belladonna after meals. There has been no recurrence of the symptoms during the ten months since discharge. This is the longest period that he has been free of discomfort for three years.

CASE 7.—*Pathology of the Esophagus Simulating Angina Pectoris.*

W. D., a physician, aged thirty-seven years, while running up two flights of stairs two steps at a time, developed a sharp, choking pain under the middle of the sternum. There was no radiation of this discomfort, and after resting for "a second or so" it disappeared. Following this episode, he experienced the pain many times a day, frequently with exertion, and frequently while resting quietly. Physical examination was negative. Electrocardiogram was normal.

Comment.—The momentary nature of the discomfort, together with the fact that it came on just as frequently while at rest as during exer-

tion, made it seem unlikely that the symptoms were cardiac in origin. The patient's age, the character of the discomfort and the lack of radiation were also somewhat against this diagnosis. The patient, however, thought that it might be angina, for five years previously, while pushing an automobile in the cold after taking two or three cocktails, he had developed auricular fibrillation which lasted several hours.

He requested to be allowed to "exercise in the cold room." Four weeks after the onset of the symptoms he performed fifty trips (equal to approximately five flights of stairs) without any discomfort; he was told that he did not have angina pectoris. A few weeks later he noticed that the pain came on chiefly when swallowing, especially saliva. X-ray examination revealed esophagitis and two small diverticuli about the middle third of the esophagus on the posterior surface. The patient's symptoms disappeared entirely following a modified Sippy regime.

CASE 8.—*Arthritis Simulating Angina Pectoris.*

Mrs. S. S., aged fifty-six years, stated that for six months she had been experiencing a needlelike and burning pain in the chest radiating down the left shoulder and left arm. This pain usually came while walking, was most commonly felt during cold weather, was associated with shortness of breath and disappeared a few minutes after she stopped and rested. In addition, she had pain and stiffness of the fingers of both hands.

Physical examination was essentially negative. The blood pressure was 160/80, and there was slight cyanosis of the lips.

Comment.—The clinical history suggested angina pectoris as the most likely cause of the symptoms. On observation during exertion, it was evident that the pain was experienced in the region of the fifth and sixth interspaces *between the anterior and posterior axillary lines* on the left and also on the *posterior aspect of the left arm.* It was also evident that this pain came not on exertion but on motion. Bending of the trunk was sufficient to induce the pain in the chest, while bending of the head brought on the pain in the shoulder and the left arm.

It was evident that this patient did not have angina pectoris. The pain was due to pathology in the spine, similar in character to the atrophic arthritis in the hand.

CASE 9.*—*Arthritis Simulating Angina Pectoris.*

Mr. H. T., aged fifty-four years, had been troubled by pain in the chest radiating to the outer aspect of both arms for about two years. The discomfort usually came on at night while in bed and woke him from sleep. It was unassociated by shortness of breath or sweating and was never induced by walking or climbing stairs. The attacks usually occurred several times a week, lasted from a few seconds to ten or fifteen minutes. A physician prescribed nitroglycerin which gave him considerable relief, and at one time an operation was advised for relief of this heart pain.

Physical examination revealed moderate arteriosclerosis, the heart size was shown to be within normal limits by x-ray examination; the electrocardiogram was normal.

Comment.—This was apparently a case of angina pectoris, but exercise in the cold room failed to produce any precordial discomfort. Sub-

*This case has been reported previously by Dr. S. Hanflig.

cutaneous injection of adrenalin induced a rise in blood pressure and a severe pain above the left breast, radiating to the left shoulder down the arm to the elbow. This was not relieved by lactose tablets but was relieved by nitroglycerin. This attack was in all likelihood angina pectoris, but the attacks which he experienced in daily life were different in character. X-ray films of the cervical and the dorsal spine revealed slight lipping about the anterior margins of the fourth and fifth cervical vertebrae. Motion of the head brought out pain in the affected regions. It seemed evident that the patient was suffering not from angina pectoris but radiculitis due to arthritis of the cervical spine. The apparent relief by nitroglycerin was seemingly against this diagnosis, but it was soon found that tablets of lactose under the tongue gave as rapid relief as did nitroglycerin.

The cervical spine was stretched and manipulated according to the method outlined elsewhere,[11] with complete but temporary relief from the symptoms. Repeated orthopedic treatment has been necessary on several occasions during the past few years. The patient has at times shown evidences of arthritis in the left shoulder and both hands.

CASE 10.—*Angina Pectoris and Cholelithiasis.*

Mrs. D. K., a forty-two-year-old housewife, was admitted to the hospital because of "indigestion." Eighteen years ago, she had a fainting spell, following which she developed a burning pain in the right upper quadrant which radiated to the region of the right shoulder blade. For three or four days she vomited frequently and required morphine for relief of the pain. During the next year the discomfort returned at frequent intervals and prevented her from working. Thirteen years ago she experienced belching and distress in the upper abdomen for several weeks. On one occasion she fainted. A diagnosis of gastric ulcer was made. Operation revealed no gastric lesion, but a pathological gallbladder was drained, following which treatment she was free from discomfort for some time. Nine years ago she developed nausea and an "annoying, dull, tearing" pain in the right upper quadrant which was accentuated by exertion and relieved by rest. X-ray studies revealed adhesions in the region of the gallbladder and duodenum. Operation was refused. Four months ago she again developed cramping, nagging pains in the right upper quadrant, coming on about three hours after meals, and accompanied by a sensation of pressure under the heart which took her breath away. At times these pains would radiate to the left shoulder and down the left arm.

Physical examination was essentially negative. The patient was well developed, short, and stocky. The blood pressure was 120/80. The blood and urine were normal; serum cholesterol, 291; electrocardiogram revealed flat T_1 and low T_2. Oral cholecystogram revealed a faint gallbladder shadow with a calcified stone in the fundus.

Comment.—The history was consistent with gallbladder disease except for the radiation to the left shoulder and left arm. Careful questioning revealed that the patient really had two types of discomfort—pain and distention in the epigastrium and right upper quadrant which usually lasted for hours and which she had had off and on for years; and pain and pressure in the region of the cardiac apex, at times radiating to the left shoulder and arm, which would last about five minutes

and which she had had for about four months. These latter attacks came on at times following the prolonged pain in the right upper quadrant, and they also came with exertion and emotion when the right upper quadrant pain was absent. The patient naturally believed that all these symptoms were due to her gallbladder and only by careful questioning as to the duration, character, and mode of onset was it possible to separate the two groups of symptoms.

After forty trips over the two-step staircase in the cold room, the patient developed a sense of pressure over the region of the cardiac apex, which did not radiate and which continued for about forty-five seconds after stopping the exercise. This sensation was typical of some of the less severe attacks which she had experienced at home and was entirely different from the symptoms in the right upper quadrant.

A diagnosis of cholelithiasis and angina pectoris was made. The patient was operated upon, and a diseased gallbladder was removed.

Reexamination a year later revealed that the pain in the right upper quadrant had disappeared following the operation, but the pain in the chest and left arm had become more frequent. It was precipitated by walking, emotion, and coughing. Exercise in the cold room again precipitated an attack of angina pectoris which radiated to the inner aspect of the left arm and was similar in all respects to that which she experienced when at home.

CASE 11.—*Angina Pectoris Associated With Diaphragmatic Hernia and Morphine Sensitivity.*

Mrs. B. B., a fifty-two-year-old housewife, had had hypertension for twenty-five years, nocturia, occasional dizzy spells, spots before the eyes, ringing in the ears, and severe headaches for ten years. Thirteen years ago her gallbladder was removed. Beginning nine years ago, she began to experience sudden severe attacks of precordial pain brought on by exertion or "aggravation" or following a heavy meal. These usually lasted about five to ten minutes and were frequently accompanied by nausea and vomiting. On three of four occasions these attacks had been very severe, were associated with a fall in blood pressure, required injections of morphine for relief, and were treated by prolonged rest in bed. For many years she had had swelling of the ankles toward evening, and on several occasions during the past three years had been awakened from sleep by shortness of breath.

Physical examination revealed the patient to be obese. There were moderate cardiac enlargement and a soft systolic murmur at the aortic area. The blood pressure was 190/100. The liver was palpable two fingerbreadths below the costal margin. There was minimal pitting edema of the legs. The lungs showed râles at both bases. The urine and blood were normal; serum cholesterol was 378 mg. per 100 c.c.; basal metabolic rate, -20 per cent. X-ray examination of the chest revealed calcification of the aorta. Electrocardiographic tracing showed deep S_2, inverted T_2, elevated $S\text{-}T_4$, with late inversion.

The excitement of coming to the hospital precipitated a severe attack of precordial pain for which she was given morphine. Shortly thereafter she vomited, the pain returned and morphine was again administered. Vomiting continued for several days, and the vomitus and stools revealed occult blood. When morphine was discontinued, the vomiting soon ceased.

Comment.—It was evident that the patient had hypertensive and arteriosclerotic heart disease with angina pectoris and mild congestive failure. The atypical feature was the frequent occurrence of vomiting with the attacks of heart pain. Exercise in the cold room precipitated an attack of precordial pain similar to that experienced at home but not accompanied by vomiting. X-ray films of the gastrointestinal tract revealed a diaphragmatic hernia.

The vomiting was apparently due to the diaphragmatic hernia and sensitivity to morphine. Severe attacks of angina were frequently treated by morphine, which in turn caused vomiting. The discomfort of nausea and vomiting would frequently precipitate other attacks of angina. As a result, the patient was unable to differentiate between the different two groups of symptoms.

UNUSUAL CLINICAL MANIFESTATIONS OF SUBACUTE BACTERIAL ENDOCARDITIS*

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THE three cases here reported are given in some detail because of their unusual clinical interest. In one, pericarditis was present at the same time as subacute bacterial endocarditis, bringing up the moot question of the relationship between active rheumatic infection and subacute bacterial endocarditis. Post-mortem examination showed that the pericarditis was due to a perforation of a mycotic aneurysm of the sinus of Valsalva with extension of the infection to the pericardium and that it was not due to active rheumatic involvement. In the second, a triad of rare findings occurred in the same patient—auricular fibrillation before the onset of the bacterial endocarditis, polycythemia, and a spleen which was not palpable at any time during the course of the disease. The third was admitted to the genito-urinary service for perinephritic abscess, but was in reality a case of subacute bacterial endocarditis with splenic infarction. When the infarct became infected the patient developed a subphrenic abscess with perforation of the diaphragm and left-sided empyema.

CASE 1.—I. S., a male, aged twenty years, student, was admitted Aug. 16, 1936 because of cough and substernal oppression for several days. The patient had migratory polyarthritis in 1926 and rheumatic endocarditis in 1929 (when mitral stenosis, mitral insufficiency, and aortic insufficiency were diagnosed). In 1933 he suffered a recurrent attack of endocarditis. He was well enough between his periods of illness to lead an active life. Two weeks before his present admission he complained of a stiff neck and a fever of 102° F. He later developed a slightly productive cough and a sensation of pressure over the precordium for two days before admission.

Physical Examination.—The patient appeared acutely ill, cyanotic; temperature was 103.6; pulse, 126; respirations, 34. The head bobbed with each heart beat. The neck showed no tracheal deviation or tug. Lungs: There were diminished breathing, dullness and râles at the left base; other areas were normal. Heart: The heart was markedly enlarged to the left. A double aortic murmur was heard at the base and a blowing systolic with an early diastolic murmur (probably transmitted from the base) could be heard in the mitral area. The rhythm was regular, the rate, 125. Blood pressure was 120/0. The abdomen was negative; no edema was present, no petechiae, and only slight clubbing of the fingertips.

Laboratory Findings.—Repeated specimens of urine showed specific gravity up to 1.024 with a rare granular cast, and an occasional faint trace of albumin. A few red blood cells were found in 4 of 24 specimens (during the first week of his stay).

The blood never showed a true anemia (5,580,000 red blood cells with 98 per cent hemoglobin on admission; 4,180,000 red blood cells with 80 per cent hemoglobin

*From the Medical Service of the Beth Israel Hospital.

three days before death). The white blood count varied between 8,350 and 13,600; the sedimentation rate between 45 mm. and 23 mm. fall in forty-five minutes. The venous pressure was 2 cm. Blood culture showed between 2 and 75 colonies of *Streptococcus viridans* per cubic centimeter. Pericardial fluid on September 12 and October 2 showed no organisms and no growth on culture. Blood Wassermann reaction was negative; blood chemistry normal.

Electrocardiogram (August 17) showed right axis deviation with slurring and notching of QRS in Leads I and III, sugesting myocardial damage.

Roentgenogram (August 28) showed marked accentuation of the ascending aorta and the left ventricular contour; no accentuation of left auricular or pulmonary conus. The apex extended to within a short distance of the axillary line. The cardiac silhouette was that of an aortic lesion, predominantly aortic insufficiency. There was no evidence of pericardial effusion.

Course.—It was felt on admission that the patient might be suffering from recurrent rheumatic carditis, particularly in view of typical Ewart's breathing at the left base posteriorly, probably due to pericarditis with effusion. At the same time blood cultures continued to show *Streptococcus viridans* in increasing number, definitely establishing the case as one of subacute bacterial endocarditis. The patient soon began to show signs of diffuse embolization (petechiae, etc.).

The bronchial breathing at the left base became more and more marked so that a diagnostic pericardial tap was performed (September 12), which yielded 30 c.c. of straw-colored fluid. The culture of this fluid was negative, the cell count 430 per cubic centimeter with 90 per cent polymorphonuclears and 10 per cent lymphocytes. Although this did not change the signs at the left base, a distinct pericardial friction rub was audible over the sternum the next day. The patient at this time developed a patch of bronchopneumonia in the right middle lobe. He began to show signs of peripheral collapse and circulatory failure. On September 21 there was marked costovertebral tenderness, probably due to renal infarcts. Three days later he had an episode of abdominal pain and rigidity in the left upper quadrant, interpreted as indicating splenic infarction. The spleen, however, was not palpable at any time, even though there was exquisite tenderness in the left upper quadrant. The area of dullness and bronchial breathing in the left chest posteriorly now began to reach a higher level. On the second pericardial tap (October 2) 150 c.c. of serous fluid were removed; this showed 420 cells per cubic centimeter, 73 per cent polymorphonuclears, 27 per cent lymphocytes, specific gravity 1.008. A loud friction rub was heard anteriorly after the pericardial tap. Gallop rhythm superseded the normal. The patient died on October 10, 1936, about eight weeks after admission.

AUTOPSY REPORT (DR. A. PLAUT)

Diagnosis.—Old and recent aortic endocarditis with valvular aneurysm and insufficiency of the aortic ostium. Mitral endocarditis with insufficiency of the ostium. Acute pericarditis. Dilatation and hypertrophy of heart, notably of left ventricle. Infarcts in spleen and kidney.

Heart.—The heart weighed 980 gm. On the anterior left ventricular surface was an area 2 cm. in diameter with a number of small, light yellowish-gray, friable tags adherent to the surface. The heart was enormously dilated and hypertrophied, especially on the left. The right auricle and ventricle were dilated. The pulmonic ring was widened; otherwise the valve appeared normal. The mitral ring was 17 cm. in circumference. The chordae tendineae were extremely long, thickened, and fused together. Some of the chordae contained minute, grayish-pink, verrucous vegetations; a row of small verrucae lay along the closure line of the valve. The aortic ring was greatly widened, the valves were thickened and fused along the com-

missures. They bore large, hard, rough, gray, vegetations. There was an aneurysm of the sinus of Valsalva of the posterior aortic cusp. The myocardium was moderately firm, pale purplish. No focal lesions were found. The left ventricular wall was 20 mm. thick, the right, 5 mm. The coronaries were wide and thin-walled. Directly below the aortic ring an indistinctly outlined, partly calcific, partly soft yellow area, 1.5 cm. in diameter, was seen. The *aorta* was quite elastic and contained many small atheromatous plaques in the ascending and thoracic portions about the openings of the vessels. *Microscopically:* No rheumatic lesions were found in the heart. The inflammatory lesions were uncharacteristic. The subepicardial fat tissue was infiltrated with small round cells. Small and large foci of granulation tissue were found scattered throughout the myocardium. The valvular lesions consisted of accumulations of leucocytes, fibrinoid necrosis of connective tissue, and some proliferation of endothelial cells and fibroblasts. The abscess-like focus below the aortic ring contained calcific material and uncharacteristic inflammation. There was moderate diffuse fatty change in the myocardium.

Lungs.—The lungs appeared edematous and hyperemic. The pleura was smooth and glistening.

Spleen.—The spleen weighed 300 gm., and was large and firm. It contained infarcts and recent infarct scars.

Kidneys.—The left kidney weighed 180 gm., the right, 160 gm. The capsule, cortex, and medulla appeared normal. There were several depressed scars due to fresh infarcts. Microscopically no Loehlein lesion or other important glomerular lesion was found.

Pelvic Organs.—Suprarenal; Stomach, and *Intestines* were normal. The *Liver;* stasis with poor definition of the acinar structure due to central atrophy.

DISCUSSION

The autopsy confirmed the clinical diagnosis of pericarditis, but this was evidently due to extension of the infective process from the mycotic aneurysm of the sinus of Valsalva to the pericardium and not to active rheumatic infection, as the absence of Aschoff bodies at post-mortem examination showed. It must be admitted that the pericarditis was interpreted clinically as probably due to recurrent rheumatic infection and not to the relatively rare condition that the autopsy revealed. It should be stressed here that this cause for pericarditis in a patient with bacterial endocarditis is not as rare as we formerly believed. Dr. Klemperer* demonstrated the organs of a case of subacute bacterial endocarditis very similar to our own. The patient, a man of fifty-three years, had clinical evidence of pericardial effusion, aortic disease, and subacute bacterial endocarditis. At autopsy no Aschoff bodies were found, but an acute pericarditis was present due to a mycotic aneurysm of the sinus of Valsalva that had penetrated deep down and involved the pericardium. Dr. Klemperer recalled two more cases that had severe ulcerating lesions of the aortic valve giving rise to pericarditis. We must think then of this lesion when we find frank signs of pericarditis in a case of subacute bacterial endocarditis not showing any manifestations of active rheumatic infection.

*Mount Sinai Hospital Pathological Conference Oct. 24, 1936. Case No. 10,006.

It is important to note that if no autopsy had been performed in this case the final clinical diagnosis would in all probability have been rheumatic pericarditis (i.e., an active rheumatic infection) in the presence of subacute bacterial endocarditis. We believe that this is an infrequent occurrence clinically, although there have been many references to the closer association of these two conditions.[1, 2, 3] The stand that the usual subacute bacterial endocarditis is implanted on recently active rheumatic lesions and not on the basis of old or healed rheumatic valvular lesions has lately been taken very effectively by von Glahn and Pappenheimer.[4] In 26 consecutive patients with subacute bacterial endocarditis (of all ages) which they report, 46 per cent showed Aschoff bodies post mortem. This is about the same proportion as in uncomplicated rheumatic carditis.[2c] We do not know from the article whether these subacute bacterial cases gave clinical as well as pathological evidence of rheumatic activity. It appears as if pathologically the two conditions occur with greater frequency than they are suspected clinically, possibly because the presence of subacute bacterial endocarditis overshadows the clinical manifestations of active rheumatic endocarditis. It is interesting to note that in the case here reported the situation was exactly the reverse, the presence of pericarditis was interpreted as indicative of active rheumatic infection, while pathologically the evidence for active involvement of the heart was absent. Perhaps it may be said, as Saphir and Wile[3] have shown, that in the younger age groups bacterial endocarditis is often engrafted on a fresh endocarditis. In the older age groups, and where a long period of time separates the known rheumatic infection and the advent of bacterial endocarditis, it is more likely that the bacterial endocarditis is implanted on a *chronically* injured valve. From the clinical point of view, however, it is not common to find frank clinical evidence of active rheumatism in a case of subacute bacterial endocarditis, and even the presence of pericarditis is not necessarily indicative of active rheumatic involvement of the heart in a case of subacute endocarditis.

It should be noted finally that there was not at any time evidence of anemia in this case of subacute bacterial endocarditis. On admission the red blood count was 5,580,000 with 98 per cent hemoglobin; and 4,180,000 with 80 per cent hemoglobin terminally. This was not due to dehydration or increased concentration of blood. Case 2, also failed to show anemia until the very last few weeks.

CASE 2.—J. R., male, aged thirty-five years. The patient had pancarditis in 1917, and recurrent fever the following year. He thought he had made a complete recovery, and felt well until four days before his first admission (Feb. 16, 1936) when he complained of low-grade fever, weakness, and general malaise. At this time he had an enlarged heart and auricular fibrillation. Laboratory: red blood cells numbered 7,080,000 with hemoglobin 110 per cent. White blood count was 8,600 with 74 per cent polymorphonuclears and 3 per cent macrophages. Sedimentation rate 14 mm. fall in 45 minutes. There were no red blood cells in the urine. Blood culture

showed 24 colonies of *Streptococcus viridans*. There were no other clinical manifestations of subacute bacterial endocarditis, such as embolization or petechiae. The five months' interval between admissions was spent mainly in bed because of persistent fever, cough, and weakness. During this entire period there were no skin lesions, weight loss, or night sweats. He was readmitted July 22, 1936 because of chest pain of three days' duration.

Physical Examination.—On readmission the patient appeared chronically ill, but well nourished. Temperature was 101° F.; pulse, 120; respirations, 26. There was no clubbing of the fingers; no petechiae. The heart was enlarged to the left. Auricular fibrillation was present with no pulse deficit. Systolic and diastolic murmurs were heard at the apex. The lungs were negative. The spleen and liver were not palpable.

Laboratory Findings.—A typical urine specimen (February 22) showed specific gravity 1.020; albumin, faint trace; 4 to 6 red blood cells and 3 to 4 white blood cells per high-power field; occasional hyaline cast; red blood cells were present in 8 of 12 urine specimens examined. The red blood count had fallen from the previous admission to 4,370,000 with 73 per cent hemoglobin on July 22. Shortly before death (September 13) the red blood count was only 3,420,000 with 65 per cent hemoglobin. There were 12,450 white blood cells, 83 per cent polymorphonuclears and 2 per cent macrophages. Sedimentation rate (July 23) 52 mm. in 45 minutes. Blood culture on 4 occasions showed 100 to 300 colonies per cubic centimeter. Blood Wassermann reaction was negative, blood chemistry, normal.

Electrocardiogram (July 23) showed auricular fibrillation. On August 24 an electrocardiogram showed frequent ventricular premature contractions in addition.

Roentgenogram at the bedside (July 31) showed the cardiac contour to be that of double mitral valvular lesion. There was a diminution in aeration in the lower half of the left lung field, but no definite evidence of infiltration or consolidation of the lungs.

Course.—The day after admission (July 23) petechiae appeared on the soft palate, which lasted forty-eight hours. Several days later he had extreme pain in the lower left chest radiating to the left shoulder, heralding infarction of the spleen. Soon after this the patient complained of abdominal pain and distention, probably due to embolization of some intestinal vessel. On August 21 there was a recurrence of pain in the left lower chest made worse by deep inspiration, suggestive of fresh splenic infarction. On September 5 edema of both ankles, a tender, distended liver, and a marked pulse deficit appeared. With active digitalization the cardiac failure was cleared somewhat. On September 11, however, pain in the lower left chest recurred and a definite friction rub could be heard over the spleen, due to a perisplenitis. Râles appeared at both bases, and respiratory difficulty rapidly increased. The patient died on September 19, two months after his re-admission. No autopsy was done.

DISCUSSION

On the first admission the patient demonstrated several findings that are unusual for subacute bacterial endocarditis. These were the polycythemia (7,080,000 red blood cells with 110 per cent hemoglobin), the presence of auricular fibrillation, the absence of a palpable spleen. To come across such a triad in a case of bacterial endocarditis is rare indeed and made us doubt the diagnosis until the further clinical course justified it.

On the second admission (July 22) the red blood count was 4,370,000 with 73 per cent hemoglobin. This should be considered a relative anemia and a marked fall in the red blood cells when compared with the original counts in February, 1936. Towards the last weeks of the patient's life the blood showed a true anemia, as might be expected in a case of bacterial endocarditis (3,420,000 red blood cells with 65 per cent hemoglobin).

The presence of auricular fibrillation at the beginning of the clinical manifestations of subacute bacterial endocarditis is rare indeed. It is a good practical dictum, stressed by many clinicians,[1, 5-8] that a fibrillator is spared the advent of a complicating bacterial endocarditis. Sprague[9] reports an interesting case which disproves this rule, as do de la Chapelle and Graef.[10] In Segal's[11] review of 192 cases of bacterial endocarditis three instances of auricular fibrillation were described. In only one, however (Case 3), was the fibrillation present before the development of the subacute bacterial endocarditis, and this is the only case that resembles our own. In the others the fibrillation occurred for a short period towards the end of the disease.

The absence of a palpable spleen throughout the clinical course of the disease in this patient is to be noted. Although Blumer[5] in his excellent review of the literature says an enlarged spleen was present in only 74 per cent of the cases, he was speaking mainly of single examinations. On the wards of Beth Israel Hospital we have been able, in the great majority of cases to palpate an enlarged spleen at some time during the disease; surely in more than 90 per cent. Unfortunately an autopsy was not permitted in this patient so that we do not have definite knowledge about the size of the spleen. Note, however, that the spleen was not palpable in Case 1 of this report, and here autopsy showed an enlarged, infarcted, spleen. It is likely that the same thing occurred in this second case—that repeated infarctions with concomitant perisplenitis made the spleen less movable on deep inspiration, so that it could not be palpated.

CASE 3.—B. M., a male milliner, aged twenty-five years, was admitted, Nov. 6, 1934, to the genito-urinary service because of sudden severe sticking pain in the left flank radiating to the left costal border four weeks before admission, followed by fever rising to about 102° F. at night. Anorexia and weight loss (35 lb. in four weeks) developed. One week before admission the patient voided reddish urine frequently for several days.

Physical Examination.—The patient appeared acutely ill and emaciated. Temperature was 105° F.; pulse, 110; respirations, 30. Lungs were negative. The heart was slightly enlarged to the left. A high-pitched diastolic murmur was heard in the aortic area transmitted to the left border of the sternum as far as the apex. The blood pressure was 145/65. There was rigidity and tenderness in the left flank as far as the costovertebral angle.

Laboratory Findings.—A typical urine specimen (November 6) showed specific gravity 1.025, albumin faint trace; 10 to 20 red blood cells, and 6 to 8 white blood

cells per high-power field; no casts. The blood showed (November 6) 4,000,000 red blood cells, 85 per cent hemoglobin, white blood cells 12,000 with 79 per cent polymorphonuclears. This rose to 44,000 with 96 per cent polymorphonuclears on November 19 when empyema developed. Blood smear from the ear lobe (November 17) showed 3 per cent macrophages. Blood cultures (November 17 and 19) were sterile. Urine culture was negative for tubercle bacillus colonies. Blood Wassermann reaction was negative. Blood chemistry showed nonprotein nitrogen 66 on November 7, and 31 on November 12.

Electrocardiogram (November 21) showed sinus tachycardia with low amplitude T_1 and T_2, suggesting myocardial damage.

Roentgenogram of the chest (November 16) showed effusion in the lower portion of the left pleural cavity with deviation of heart to the right. There was exaggeration of the right and left cardiac contours.

Course.—From the history, it was believed at first that the patient was suffering from a perinephritic abscess. Cystoscopy revealed turbid urine in both ureters with many red blood cells and white blood cells. The concentrating power was not impaired, however. Pyelographic examination of the urinary tract was entirely negative, showing no evidence of perinephritic abscess or urinary calculus. The patient continued to run fever for a week. On medical consultation, signs of frank pleurisy at the left base were found. In addition to the aortic diastolic murmur a mitral systolic and diastolic were now heard. The edge of the spleen was palpable. It was considered that the presence of fever, a palpable spleen, and hematuria in a case of valvular heart disease (aortic) pointed strongly to the diagnosis of subacute bacterial endocarditis. The effusion in the chest following a bout of pain in the left flank suggested a splenic infarct with subsequent suppuration which had extended to the left pleural cavity. The blood culture was negative; but there were 3 per cent macrophages on blood smear. The signs of fluid in the left chest increased and aspiration revealed a sanguino-purulent fluid. On rib resection the left diaphragm was found very high. While exploring the empyema cavity an opening was made through the softened diaphragm into a pocket of subdiaphragmatic pus. The exact location of this pus could not be determined because of the precarious condition of the patient. Following operation the patient continued to do poorly in spite of blood transfusion. He finally succumbed six days after operation; about three weeks after admission.

AUTOPSY REPORT (DR. A. PLAUT)

Diagnosis.—Empyema of left pleural cavity. Perforation of left dome of diaphragm leading into broken-down splenic infarct. Perisplenic adhesions. Aortic endocarditis with insufficiency. Circumscribed mitral endocarditis with formation of so-called valvular aneurysm. Dilatation and hypertrophy of left ventricle. Kidney infarct. Glomerulonephritis, partly of the embolic bacterial type, partly true Loehlein lesion.

Heart.—The heart weighed 323 gm. The left ventricle was wider than normal. One centimeter above the free edge of the mitral commissure a very soft, hyperemic mass 1.5 cm. in diameter protruded, attached to the valve by a broad base. There were soft, purplish-gray vegetations on the ventral surface of the valve. A small hole in the center formed a so-called valvular aneurysm. The aortic leaflets were the seat of an old endocarditis. They were shortened and thickened; the free edges had a moth-eaten appearance and had fine reddish masses upon them. One centimeter below the base of the right cusp there were irregularly crescent-shaped thickenings in the endocardium of the septum. The ascending aorta was slightly atheromatous, otherwise normal. The inside of the sinus of Valsalva showed nothing remarkable. The coronary arteries were wide and normal. The auricles, the pulmonary and

tricuspid valves, and the myocardium of the right side showed nothing abnormal. *Microscopic:* The section from the aortic valve does not show recent endocarditis. Crushed smear from vegetation of heart valve shows numerous gram-positive streptococci in chains of 4 to 6.

Lungs.—Bronchi, arteries, and lung tissue were normal, except for slight emphysema.

The *spleen, pancreas, stomach,* and the *left dome of the diaphragm* formed a large, irregular soft mass. At the highest point of the left dome of the diaphragm there was a rough circular opening about 7 cm. in diameter leading into an irregular cavity with torn bloody walls, and irregularly torn splenic tissue. It was separated from the diaphragm by fat tissue. Smaller infarct-like areas were seen at different points. Fibrin-like masses could be seen when the adherent diaphragm was partly removed from the surface of the spleen. An abscess the size of a small almond was situated within the diaphragm. The *liver,* which weighed 2,040 gm., was hyperemic and showed some fatty changes.

Kidneys.—The kidneys were large, and stripped easily from the capsules. The left kidney contained a yellow, roughly wedge-shaped nonprotruding corpus with a hyperemic marginal zone. *Microscopic:* The yellow focus was an infarct. The glomerular pictures varied considerably. Some glomeruli were almost normal, some showed the capsular changes of glomerulonephritis, while other glomeruli gave a characteristic picture of a Loehlein lesion.

DISCUSSION

There are several points of interest in this case. The initial reference of the patient to the genito-urinary service rather than the medical is not an infrequent occurrence when the presenting symptoms are high intermittent fever and hematuria. We have seen this error made several times before. The diagnosis of subacute bacterial endocarditis could not be confirmed ante mortem in this patient because the blood culture was sterile. The differential diagnosis was mainly between perinephritic abscess and splenic infarction with secondary infection in a case of subacute bacterial endocarditis. Aside from the negative pyelographic findings and the positive findings in the heart, several other considerations pointed to the latter diagnosis. Elevation of the diaphragm is not common in perinephritic abscess, while it is the rule in subphrenic. The pain in the left upper quadrant radiating to the left costal margin pointed to a perisplenitis such as one sees in infarction rather than a kidney lesion. Splenic infarction is likely to occur terminally and not as the early clinical manifestation of subacute bacterial endocarditis that this case showed. From the history it appears that the splenic infarction occurred during the first month and that the patient did not die directly from the subacute bacterial endocarditis but rather from a complication of the disease—a secondary infection of a splenic infarct. There was frank pus in the splenic abscess which was evidently due to a secondary infection, for the *Streptococcus viridans* (recovered from the heart valves) is not a pus-producing organism and could not in itself have been responsible for the pus found in the spleen, diaphragm and left pleural cavity.

SUMMARY AND CONCLUSIONS

Three clinically unusual cases of subacute bacterial endocarditis are reported. In one a pericarditis was present concomitantly with subacute bacterial endocarditis. The pericarditis was clinically believed to be a manifestation of active rheumatic infection—at autopsy it was found to be due to an extension of infection from a mycotic aneurysm of the sinus of Valsalva to the pericardium. This cause for pericarditis in a patient with subacute bacterial endocarditis is not as uncommon as formerly believed. The question of the relationship between active rheumatic infection and subacute bacterial endocarditis is discussed. Their simultaneous presence occurs oftener in children apparently than in adults.

The second case is one in which auricular fibrillation preceded the subacute bacterial endocarditis and persisted throughout its course. This is contrary to the clinical dictum which has been considered almost axiomatic—that fibrillation spares the patient subacute bacterial endocarditis. The case also failed to demonstrate a palpable spleen throughout the entire course of the illness, even though there was clinical evidence of repeated splenic infarctions. When the subacute bacterial endocarditis was first detected in this patient he had a secondary polycythemia (7,080,000 red blood cells with 110 per cent hemoglobin). For fully five months of the illness he suffered a relative, but not an absolute anemia. The combination of three such rare findings as fibrillation, a nonpalpable spleen and a polycythemia in a patient with subacute bacterial endocarditis is considered worth noting.

In the third case which was mistaken at first for perinephritic abscess because of intermittent fever and hematuria, autopsy showed that the patient had bacterial endocarditis and a splenic infarct which had become secondarily infected. The abscess broke through the diaphragm and caused a fatal empyema. The cardiac murmurs, palpable spleen, and the subphrenic involvement pointed to the correct diagnosis.

The authors are deeply indebted to Dr. Isidore W. Held for his invaluable aid in the clinical observations of these patients.

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SUBACUTE BACTERIAL ENDOCARDITIS

Clinicopathological Study of Thirty-Seven Cases*

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SUBACUTE bacterial endocarditis continues to be one of the most dreaded diseases, especially to that group of patients who have a mild chronic rheumatic lesion of the heart and who would otherwise enjoy several years of fairly good health. Davis and Weiss[1] have estimated that about one of every ten patients having rheumatic heart disease will acquire subacute bacterial endocarditis. Thus, it is possible to see what a menace it is to this particular group. Thirty-seven cases of subacute bacterial endocarditis in which necropsy was performed form the basis of this report.

Age and Sex.—The decade of greatest incidence varies in different series of cases. Clawson[2] found about an equal incidence in the third, fourth, and fifth decades of life. Davis and Weiss observed that in the largest number of their cases the patients had acquired the disease in the fifth decade, while Fulton and Levine[3] found that the disease most frequently occurred in the third decade of life. In twelve (32 per cent) of the thirty-seven cases which form the basis of this report, the patients had acquired the disease in the fourth decade of life, and in the remainder of the cases the age of the patients varied; the youngest patient was ten years and the oldest was sixty-seven years of age.

Rheumatic heart disease is more prevalent among females than it is among males. It, therefore, would seem logical to expect that the incidence of subacute bacterial endocarditis also would be more prevalent among females. This, however, has not been true in other series of cases which have been reported in the literature. Nor was it true in the

Table I

Incidence According to Age and Sex

	Patients	
Age, Years	Males	Females
−1 to 9	0	0
10 to 19	1	3
20 to 29	4	3
30 to 39	9	3
40 to 49	4	2
50 to 59	2	0
60 to 69	5	1
Total	25	12

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series of cases which we have observed, as twenty-five of the patients were males and twelve were females; in other words, the ratio of males to females was approximately 2 to 1 (Table I).

Bacteriology.—The *Streptococcus mitior* (*Streptococcus viridans*) is the most common etiologic agent. In twenty-nine cases the blood culture yielded a growth of *Streptococcus mitior;* in five cases the blood culture did not reveal any growth; and in the remaining three cases the cultures yielded *Diplococcus pneumoniae,* type I, *Diplococcus pneumoniae,* type II, and *Proteus ammoniae,* respectively.

Other Laboratory Data.—The Wassermann reaction on the blood serum was positive in four cases, but necropsy in these cases failed to disclose any syphilitic lesion of the heart or aorta, on which a subacute bacterial endocarditis might have been superimposed.

The erythrocyte count in all cases except three was materially reduced at the time the patients were first examined at the clinic. In twenty of the thirty-seven cases the number of erythrocytes ranged between 3,000,000 and 4,000,000 per cubic millimeter of blood. In the remainder, except the three cases mentioned previously, the number of erythrocytes was less than 3,000,000 per cubic millimeter of blood. The number of leucocytes varied from 2,600 to 38,000 per cubic millimeter of blood. Leucopenia has been reported frequently, but because most of the patients in this series of cases were seen in the later stages of the disease, this finding was not noted frequently. In twenty-six of the cases the value for the hemoglobin was less than 10 gm. (60 per cent) per 100 c.c. of blood.

The specimens of urine in all cases contained some albumin, but in nine cases no erythrocytes could be found in the urine.

In eight cases the value for urea was 60 mg. or more per 100 c.c. of blood. In four of these cases death was the result of a complicating uremia; in those cases values for the urea were 411, 273, 314, and 268 mg. per 100 c.c. of blood, respectively. The renal function remains good in most cases, even though an embolic nephritis is present.[2]

Duration of Symptoms.—The insidious onset of the disease makes it difficult for most patients to tell exactly when the illness began. The total duration (from onset of symptoms to time of death) of symptoms in no case was longer than one year and in thirty cases (80 per cent) it was six months or less.

Embolic Manifestations.—Nineteen (51 per cent) patients of this group had clinical manifestations of emboli in one or more forms. Fifteen had petechiae of the skin, conjunctiva, or mucous membranes of the mouth. Five patients had hemiplegia which was the result of cerebral emboli. In seven cases petechial hemorrhages were present in the retina. One patient died of an intraperitoneal hemorrhage which was caused by a rupture of a mycotic aneurysm of the splenic artery.

Splenic Enlargement.—The idea is common that the spleen should be palpable in cases of subacute bacterial endocarditis. In twenty-four cases (64 per cent) the spleen was not definitely palpable. In only two cases of the entire group was the spleen not enlarged (200 gm. or more) at necropsy. The average weight of the spleens which were not palpable was 402 gm., while the average weight of those which could be palpated was 478 gm. Thus, in most cases the spleen was enlarged even though it was not palpable. Infarcts, recent or ancient, were present in the spleen in all cases except one.

Relationship of Chronic Valvulitis to Subacute Bacterial Endocarditis.—In nineteen (51 per cent) of the cases there was a history of rheumatic fever. In five of these cases there was no good pathological evidence of a rheumatic endocarditis. In the remaining group of eighteen cases there were seven in which there was a chronic valvulitis. Twenty-two (60 per cent) of the patients had chronic valvulitis which was indicative of a previous infection. Three had the subacute process superimposed on calcified aortic valves. The ages of these three patients were sixty-seven, sixty, and sixty-six years, respectively. The etiology of this calcareous lesion of the aortic valves was not clear. This leaves twelve cases (32 per cent) in which there was no pathological evidence of a previous valvulitis on which the subacute process might have been engrafted.

Degree of Underlying Valvular Deformity in Relation to Subacute Bacterial Endocarditis.—Sprague[4] reviewed the post-mortem and clinical findings in twenty cases of subacute bacterial endocarditis in which the mitral valve was involved and found that in none of the cases was the circumference of the valve less than 8 cm. Clinical examination revealed that only one patient had mitral stenosis (loud first sound with a presystolic murmur) and that all the others had a mitral regurgitation (loud systolic murmur). The degree of rheumatic valvular damage in forty-seven cases of subacute bacterial endocarditis studied by Davis and Weiss corresponded with that which was found in 474 cases of rheumatic valvulitis. These authors said that the mild rheumatic lesions are not involved more frequently (in percentage) than advanced rheumatic lesions since they are much more frequent. In this series of cases the mitral valve was involved by the subacute process in twenty-seven cases; in twenty of these cases there was an underlying chronic valvulitis. The average circumference of the mitral valve in these twenty-seven cases was 10 cm. In only four of these cases was the circumference of the mitral valve less than 8 cm., the measurements being 6.5 cm., 7.0 cm., 7.0 cm., and 6.0 cm., respectively. The electrocardiogram also gave some corroborative evidence. An electrocardiogram was made in thirteen of the cases of mitral subacute endocarditis and in only one of these cases was there a right axis deviation (right ventricular preponderance). Necropsy in this case revealed a mitral

valve which measured only 6 cm. in circumference. None of the electrocardiograms revealed an auricular fibrillation, which usually comes on after a stenosis of the mitral valve has been present for some time. It is not important to determine if the mild rheumatic lesions are involved more frequently (by percentage) than the stenotic lesions, but it is important to realize that subacute bacterial endocarditis shortens the lives of those who have rheumatic endocarditis and who would otherwise enjoy several years of fairly good health.

Endocardial Involvement.—The idea is somewhat prevalent that in cases of subacute bacterial endocarditis the aortic valve is attacked more frequently than is the mitral valve. This has not been true in this series. Clawson and Bell[5] have also found that the ratio of involvement of the mitral and aortic valves is about the same in subacute bacterial endocarditis as it is in chronic valvulitis. In this series of cases the mitral valve was the only one involved in seventeen (46 per cent) cases and the aortic was the only one involved in ten (27 per cent) cases. Both the mitral and aortic valves were attacked in eight (21.6 per cent) cases; the mitral, aortic and tricuspid valves were involved in one case; and the mitral and tricuspid valves were involved in one case.

The post-mortem appearance of the heart in a typical case was as follows: The heart weighed 390 gm. and was of a pale brown color. The consistency was normal and the incised surface was the same color as the pericardial surface. There was not any streaking of the myocardium. The foramen ovale was closed, and there was no evidence of coronary sclerosis. The mitral valve was the site of old endothelial thickening and the chordae tendineae of the mitral valve were short and thick. There were fresh vegetations on the chordae tendineae and along the edge of the mitral valve; these extended upward into the anterior and medial wall of the left auricle. These were pinkish, rounded cauliflower-like growths. The aortic valve measured 6 cm., and the mitral valve measured 10 cm. in circumference.

Weight of the Heart.—The weight of the heart varied from 222 gm. to 800 gm. When compared with the computed weights, as determined by the normal body weight according to the method of Smith,[6] the hearts were found to be enlarged in all except three cases. As would be expected, the largest hearts were found in those cases in which there was an aortic endocarditis.

SUMMARY

In this series subacute bacterial endocarditis was more common among males than among females. In the majority of cases the patients were in the third, fourth, and fifth decades of life. Embolic processes were common. The spleen was almost invariably enlarged, even though not palpable. The *Streptococcus mitior* was the usual etiological agent but

it was not the only one. A rheumatic infection commonly precedes subacute bacterial endocarditis. The degree of previous valvular damage is usually mild. The mitral valve is involved more frequently than is any other valve. In no case was the duration of symptoms more than one year and in 80 per cent of cases it was six months or less.

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Department of Clinical Reports

THE OCCURRENCE OF AN UPRIGHT T-WAVE IN LEAD IV IN A PATIENT WITHOUT OTHER EVIDENCE OF HEART DISEASE

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IN CHILDREN an upright T_4 is often seen without heart disease and alone bears no significance in diagnosis. In the adult, however, it has been described as a most significant finding. Statements that observers of wide experience[1] have never observed this change in the absence of "significant heart disease" justify the report of the following case.

CASE REPORT

H. O., aged twenty-six years, a white nurse, presented herself for a routine periodic health examination. There were no complaints and the patient considered herself in the best of health.

Past history revealed the following pertinent points: measles at eight years; whooping cough at ten years; and diphtheria at twelve years. The appendix was removed at the age of eighteen years. There was no history of rheumatic fever, Bright's disease, or sore throats. The venereal history was negative. Cardiorespiratory symptoms have never been noted except for a sensation of pressure in the chest, pain in the left axilla and a subjective feeling of being unable to catch her breath on one occasion a year ago. This sensation passed off in one hour and has never returned. *Personal habits* are not remarkable. She smokes rarely, but takes four to six caffeine drinks daily. *Family history* disclosed no hereditary diseases. The mother and father are living and well. *Physical examination* revealed a young white female with erect posture and sthenic habitus—height 65 inches; weight 129 pounds. Blood pressure was 128/78 in both arms; pulse, 82 per minute while sitting; after exercise (jumping 20 times on one foot) 110 per minute; after two minutes' rest 80 per minute. The thyroid isthmus was palpable. The lungs were clear.

Heart.—No pulsations were visible. The apex beat was palpated in the fifth left interspace just inside the midclavicular line. No abnormal pulsations were palpated. Percussion confirmed palpation. Basal dullness coincided with the manubrium sterni. P_2 was greater than A_2. The sounds were otherwise not noteworthy. A soft blowing systolic murmur was heard in the pulmonic area down to the third left interspace and disappeared in the left lateral position. An occasional premature beat was heard. The *abdomen* was negative. Pelvic and neurological examinations disclosed no abnormalities. Extremities were negative.

Laboratory Data.—Urine: specific gravity, 1.020; clear; negative for albumin, casts and red blood cells; occasional pus and epithelial cells. *Stools* were negative for ova and parasites. *Blood* showed red blood cells, 4.87 million; hemoglobin, 85

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per cent; white blood cells, 9,000; differential, normal. The *Wassermann* reaction was negative. The basal metabolic rate was -6 per cent. *Electrocardiogram* (Fig. 1) showed normal sinus rhythm, T_2 isoelectric; T_3 negative; T_4 upright. *X-ray film of the chest* showed that lung fields were clear. Heart measurements were: transverse, chest, 26.3 cm.; transverse, heart, 12.5 cm.; longitudinal, heart, 13.9 cm.; transverse, great vessels, 5.4 cm. *Fluoroscopy,* including that in the oblique position, with barium paste, disclosed no deviation of the esophagus and no abnormal configuration of the heart.

COMMENT

Clinically, a diagnosis of heart disease, or possible heart disease, was impossible in this patient. All physical findings, the reaction to exer-

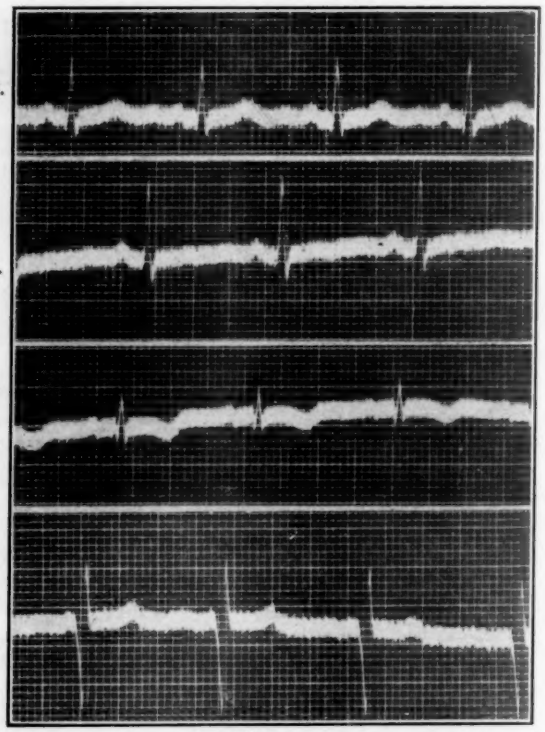

Fig. 1.

cise, as well as the reaction to usual daily activity, indicated no impairment of function. The usual pathognomonic signs of organic heart disease, such as cardiac enlargement, serious mechanismal disturbances (auricular fibrillation, auricular flutter, pulsus alternans), thrills, friction rubs, diastolic murmurs, liver enlargement and other evidences of elevated venous pressure, were absent. No etiological factors such as hypertension, arteriosclerosis, hyperthyroidism, syphilis, or rheumatic fever were demonstrable. There was no precordial pain of any type. Acute rheumatic carditis and bacterial endocarditis, diseases which may be present at this age without pathognomonic signs of heart disease, were obviously not detected. In fact, significant cardiac changes or even sug-

gestive changes were absent. Extracardiac disease known to affect the heart and electrocardiogram transiently, for example, hemorrhage, was not present. The patient, to all appearances and tests, is a perfectly normal young woman.

In the past two years the electrocardiogram has been taken three times. The chest leads have been placed accurately by the author in the two repetitions according to the technique of Wolferth.[1] There is no technical fault. The isoelectric T_2 is usually considered a suggestive sign of heart disease, but this finding again has been reported in normal individuals and cannot be considered significant.

Edeiken, Wolferth, and Wood[1] state, "We have not as yet seen an upright T_4 in an adult in whom we were at all confident that 'there was no significant heart disease' unless the patient had received digitalis." They criticize the statement of Levine and Levine[2] who reported upright T_4 in two patients without "significant heart disease" but with uremia and hemorrhage, respectively, both of which are known to produce T-wave changes. In the present patient no known cause except the possibility of an old diphtheritic myocardial lesion could be found to explain the T_4. Three examinations in two years have all disclosed the upright T_4. That evidence of heart disease may appear in the future is possible, but in two years' observation no such findings have developed.

SUMMARY

A patient without demonstrable heart disease or extracardiac disease producing T-wave changes has been known to have an upright T_4 for two years. While this finding, as the single definite electrocardiographic abnormality, should be considered highly important, it appears to occur at times in the absence of "significant heart disease."

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Department of Reviews and Abstracts

Selected Abstracts

Heckmann, K.: Graphic Recording of the Variations in Intensity of the Heart Shadow in Mitral Insufficiency Recorded With a Photoelectric Cell (Actinocardiogram). Klin. Wchnschr. **15**: 928, 1936.

The author has developed a method of recording the intensity of the shadow cast by the heart under roentgenogram on the viewing screen by means of a photoelectric cell, three-stage radio amplifier and oscillograph. This is used as an index of volume changes of the heart. In mitral insufficiency he found that the cardiac pulsations decreased, and the curve shows a systolic increase in volume (the inverse of normal) followed by a decrease. During diastole, a slight volume increase (or no change) was noted followed by a marked auricular decrease. These changes are caused by the systolic regurgitation of blood from the left ventricle into the left auricle and pulmonary vessels.

L. N. K.

Diebold, O., and Mertens, O.: Central Nervous Regulation of Cardiac Minute Output During Inhalation of CO_2 Rich Air. Pflügers Arch. f. d. ges. Physiol. **237**: 585, 1936.

The blood flow in the main or left branch of the pulmonary artery was measured with a Rein thermostromuhr and from this cardiac minute volume was determined. CO_2 in concentrations of 5 to 12 per cent in the inspired air decreased the minute output of the heart. This decrease was obtained only when the vagi were intact.

L. N. K.

Wöhlisch, E., and Clamann, H. G.: The Elastic Properties of the Resting Heart. Pflügers Arch. f. d. ges. Physiol. **237**: 590, 1936.

The author determined the curve of tension/length ratios of isolated heart muscle strips and also the curve of pressure/volume ratios of resting hearts. The ratios never gave a straight line relationship. In comparison to other muscles investigated the heart muscle had the least resistance to stretch.

L. N. K.

Goldenberg, M., and Rothberger, C. J.: Action of Veratrin on Purkinje Fibers. Pflügers Arch. f. d. ges. Physiol. **238**: 137, 1936.

Small doses of veratrin cause acceleration and increase in the size of the beat of isolated Purkinje fibers obtained from the dog's heart, and at the same time the electrogram, but not the mechanogram, is prolonged. Larger doses are the cause of paroxysms of tachycardia with pauses between. Long after-potentials are demonstrated to occur in the electrogram (similar to that in nerve and ordinary muscle).

L. N. K.

Weicker, B.: Adrenalin and Metabolism of the Warm-Blooded Heart. Arch. f. exper. Path. u. Pharmakol. **181**: 525, 1936.

In the cat's Langendorff heart with practically normal lactic acid content, adrenalin in therapeutic doses caused no change in the phosphoric acid fraction. With toxic doses an increase was found in the phosphoric acid and hoxosephosphate content (due to the breakdown of phosphagen and adenylpyrophosphate).

In the hypodynamic Langendorff heart adrenalin in therapeutic doses caused a disappearance of phosphoric acid (and a restitution of its precursors). This occurs only in the presence of oxygen and fails to occur when the heart is kept under anaerobic conditions. Strophanthin has actions similar to adrenalin.

L. N. K.

Lissak, K., and Hoyos, G.: Loss of Albumin of Working Heart Muscle. Arch. f. exper. Path. u. Pharmakol. **181**: 607, 1936.

Albumin can be demonstrated by precipitation and anaphylactic reactions in the Ringer perfusate obtained from a frog heart perfused by the method of Straub. Stimulation of vago-sympathetic fibers causes an increase in the albumin in the perfusate.

L. N. K.

Döring, G.: Experimental Production of Left Ventricular Hypertrophy by Injections of Ephedrine-Ephetonin. Beitr. z. path. Anat. u. z. allg. Path. **96**: 309, 1936.

In rabbits, subcutaneous injections of ephedrine or ephetonin (0.05 mg. per day) for several months cause chronic hypertension. This led, after 69 to 107 days, to left ventricular hypertrophy in 5 animals; this is accompanied by a right ventricular hypertrophy due to stasis in the pulmonary circuit. In acute hypertensions left-sided dilatation could be shown. In 4 animals kept on this regime for 135 to 164 days, no hypertrophy could be demonstrated. This was due to the disappearance of the hypertension after the one-hundredth day. This suggests that hypertrophy is a reversible process. (This idea requires further confirmation.)

L. N. K.

Henze, C.: The Pressor Receptor Fibers in the Vagus. Arch. internat. de pharmacodyn. et de thérap. **53**: 44, 1936.

Following section of the vagi, a rise in blood pressure can occur in an animal in which the carotid sinuses and aortic roots have been denervated previously. This is interpreted as indicating pressor fibers coming from the heart itself. The pulmonary pressure did not change under these circumstances.

L. N. K.

Sylla, A.: Slowing of the Heart With Deep Inspiration. Klin. Wchnschr. **15**: 849, 1936.

In 1,000 students slowing of the heart was found in inspiration and in inspiratory arrest. It occurred in abdominal breathing but often failed to appear with exaggerated costal breathing when the diaphragm did not move much. In certain tachycardias a similar slowing was found when the diaphragm was deeply depressed during inspiration.

L. N. K.

Alam, M., and Smirk, F. H.: Observations in Man Upon a Blood Pressure Raising Reflex Arising From the Voluntary Muscles. J. Physiol. **89**: 372, 1937.

A blood pressure raising reflex can be demonstrated in normal subjects by a simple clinical method in which a standard exercise test is used. In these experiments one extremity, usually an arm, is used in performing the test. Increases in systolic blood pressure from 5 to 85 mm. of mercury occur during the exercise test. The increase in the diastolic pressure is usually less than the increase in the systolic pressure. Various experiments indicate that the rise in blood pressure is caused by substances liberated during the muscular work and is not dependent upon the method of arresting the circulation, nor does it occur as the result of pain or mental effort. It seems that this reflex is designed so that the voluntary muscles as they become fatigued may call upon the central nervous system to regulate the supply of blood in their favor.

E. A. H.

Cossio, P., Del Castillo, E. B., and Berconsky, I.: Investigation of Blood Velocity After Exercise. Rev. argent. de cardiol. **3**: 409, 1937.

Both the circulation time of the blood (intravenous injection of 20 per cent "decholine") and the heart rate, before and after exercise (30 flexion movements of the legs in one minute), were investigated in 82 persons lying in a recumbent position: 10 entirely healthy people, 7 suffering from severe impairments other than cardiac disease (cancer of the stomach, leucemia, etc.), 6 with hyperthyroidism, and 59 with structural alterations of the heart. The magnitude of the reduction in the circulation time after exercise has been considered to be an index of the so-called reserve power of the heart, under the assumption that the heart output is the fundamental factor governing the speed of the blood flow.

In the group of 10 healthy people, the decrease in the circulation time varied from 0 to 17 per cent in three sedentary persons, and from 29.9 to 46.1 per cent (average 31.8 p. c.) in active individuals, some of them devoting much of their time to athletic activities. There was no relation between the decrease of circulation time and the increase in heart rate.

In the group of severely ill people without cardiac involvement, the reduction in the circulation time after exercise varied from 5 to 15 per cent (except in one case in which the reduction reached 23 p. c.). The heart rate increased from 20 to 75 per cent but with no relation to the decreased circulation time.

In the hyperthyroidism group, while 4 patients showed a decreased circulation time, the reduction varying from 0.6 to 26 per cent, in two cases a prolongation of the time was found, a type of reaction which we qualified as paradoxical.

Among the group of cardiac patients, in 7 the decrease in circulation time amounted to at least 27 per cent; in another 30 it was less than 25 per cent; in 7 there was no appreciable change, and in the remaining 15 patients a paradoxical reaction was observed. To explain the latter, an increased initial tension of the cardiac fiber beyond the critical value has been assumed.

AUTHOR.

Korth, C., and Schrumpf, W.: Reciprocal Rhythm. Deutsches Arch. f. klin. Med. **178**: 589, 1936.

A case of sinoauricular block is described in which the electrocardiogram showed coupled beats which are attributed by the author to reciprocal rhythm. In each pair of beats, the first is from the A-V node. It is conducted back to the auricle later than to the ventricle, and this auricular impulse then returns to restimulate the

ventricles. The conditions for reciprocal beating are fulfilled in the case described, viz.: (a) undisturbed action of an automatic A-V rhythm at a slow rate at the lower end of the node and (b) retrograde conduction.

L. N. K.

Hecht, H.: Precordial Leads in Clinical Electrocardiograms. Deutsches Arch. f. klin. Med. **179**: 1, 1936.

The author used two precordial regions for the exploring electrode (third interspace to the right of the sternum and the sixth interspace over the apex), his fixed electrode being the null point electrode of Wilson. The contour of the records in 200 normal and cardiac patients is described. In left preponderance a flattening of T was found in the apical lead; in right preponderance a reversal of all the complexes was found in the basal lead. This permitted him to distinguish between axis shift and preponderance. The value of these leads in flutter and fibrillation of the auricles is emphasized, and they show changes in S-T and T-waves early in abnormal hearts.

L. N. K.

Spühler, O.: Adams-Stokes Syndrome. Ztschr. f. klin. Med. **129**: 693, 1936.

The author finds that Adams-Stokes syndrome is caused as often by transient ventricular fibrillation as by standstill of the heart.

L. N. K.

Marzahn, H.: Electrocardiographic Studies During Work. Ztschr. f. klin. Med. **130**: 135, 1936.

When work caused an acceleration of the heart to 200 beats per minute, the author found that the QRS span was shortened by 0.01 second. Extrasystoles tended to appear, but extrasystoles present at rest tended to disappear. No difference was noted in the appearance, disappearance, and magnitude of the cardiac acceleration between normal and cardiac patients. An acceleration was found following exercise in patients with complete heart-block.

L. N. K.

Comeau, Wilfrid J.: Paroxysmal Complete Heart Block Alternating With Normal Rhythm and Conduction. Am. J. M. Sc. **194**: 43, 1937.

The literature of recurrent complete heart-block alternating with normal conduction and accompanied by Adams-Stokes syndrome has been examined critically. Of 20 potential cases discovered in the literature, 12 have been accepted as complying with the criteria established. The important clinical, pathological, and electrocardiographic data of these cases have been summarized.

A case, a woman aged seventy-eight, with Adams-Stokes syndrome, is presented in which, as shown by electrocardiographic evidence, complete heart-block alternated with normal rhythm and conduction. The results with atropine demonstrated that the changes probably occurred independent of any vagus effect. This case ultimately developed a chronic complete block with the spontaneous disappearance of the syncopal attacks.

The form of the transition from one degree of conduction to another, as shown by graphic tracings, is summarized.

The practical diagnostic and therapeutic considerations of this condition are emphasized.

The pathogenesis of paroxysmal complete heart-block is discussed. It is probable that the majority of cases are on an arteriosclerotic basis and that either a fibrocalcareous mass or fibrosis due to coronary sclerosis partially damages the bundle of His. The fluctuating character of the conduction in these cases is probably determined by temporary variations in the local circulation to the remaining intact fibers.

AUTHOR.

Grosse-Brockhoff, F., and Strotmann, A.: The Time Relation Between Mechanical Systole and the Electrocardiogram. Ztschr. f. d. ges. exper. Med. **98**: 227, 1936.

The volume curves and optical carotid artery pressure curves were recorded in anesthetized rabbits, simultaneously with Lead I of the electrocardiogram. No constant relation was found between the end of the T-wave and the end of the mechanical systole. It was found that the Q-T interval is not equal to the duration of the mechanical systole, and the ratio between the two is inconstant. One cannot judge the duration, let alone the power of systole from the electrocardiogram.

L. N. K.

Heim, F.: Conduction Disturbances in Human Heart. Ztschr. f. d. ges. exper. Med. **98**: 551, 1936.

The relation of the P-R interval to the duration of the cycle is determined and shown to give a smooth curve. It is shown that the P-R interval does not lengthen as much as anticipated following interpolated auricular extrasystoles, presumably because the refractory period is shortened as the heart rate accelerates. The Wenckebach phenomenon in the digitalized heart with A-V block is attributed to progressive lengthening of the refractory period from beat to beat until a ventricular beat is dropped and the refractory phase is shortened again.

L. N. K.

Zárday, I. V.: Electrocardiographic Studies of the Auricles. Ztschr. f. d. ges. exper. Med. **98**: 662, 1936.

The author used unipolar chest leads and could distinguish the action of each of the auricles. He demonstrated an asynchrony of 0.01 to 0.09 second between the onset of electrical activity in the two auricles. Leads I and III, according to the author, give only the P-wave of the left auricle, while the P-wave in Lead II is a summation of the activity of the two auricles. Splintering of P_2 is due to interauricular block, and this block is the cause for a difference in the P-R interval in Leads I and II. (The interesting observations need confirmation.)

L. N. K.

Lewis, Thomas: Auricular Flutter Continuing for Twenty-Four Years. Brit. M. J. **1**: 1248, 1937.

The case is of exceptional interest for three reasons. First, the auricles seem to have fluttered without cessation for twenty-four (if not twenty-seven) years. Secondly, although the ventricle during the greater part of the period has been driven at very excessive rates, the efficiency of the heart has not been impaired by its increased energy expenditure. Thirdly, the rate of auricular beating has fallen about 80 beats per minute. This fall might be attributed to lengthening of the circular path around which the wave travels, or more probably to its slower speed of movement. It would be interesting to know if lowering of rate is usual in auricular flutter as age greatly advances.

AUTHOR.

Arieff, M. J., Wituschinsky, W. J., and Rabinerson, A. B.: The Collateral Circulation of the Heart in Syphilitic Meso-aortitic Closure of the Mouths of the Coronary Arteries and in Adhesive Mediastinopericarditis. Ztschr. f. klin. Med. **130**: 153, 1936.

Collateral vessels in the heart come either from enlargement of vessels already present or from the development of new vessels. In syphilitic closure of the coronary vessel mouths, the collaterals between the right and left coronary arteries form the new vessels. In mediastinopericarditis, the new vessels come from anastomoses with extracardiac vessels, chiefly those of the lung and diaphragm.

L. N. K.

Hafkesbring, Eleanor M., Drawe, Catherine E., and Ashman, Richard: I. Measurements for One Hundred Normal Children. Am. J. Dis. Child. **53**: 1457, 1937.

To establish trustworthy criteria for the normal electrocardiogram of the child, electrocardiograms of 100 normal children were selected and the heights of the individual deflections in each lead as well as the time relations of the various intervals and phases of the cardiac cycle were carefully measured.

The duration of the P-wave was found to average 0.062 second. The upper limit we would consider to be 0.09 second or perhaps 0.085 second, since a P-wave measuring 0.09 was found in only 1 case.

Since the height of the P-wave in Lead I was slightly higher than the average for the normal adult, the upper limit should be placed at about 1.5 mm. or a little lower. A P_2 measuring over 2.5 mm. should be considered above the normal.

A diphasic or slightly inverted P_3 is occasionally found in the electrocardiogram of a normal child.

Slight and questionable notching of the P-wave is occasionally seen, but no definite or conspicuous notching of the P-wave is found in the electrocardiogram of a normal child.

The average P-R for our series was 0.132 second, and there was no significant difference according to sex. We found that the P-R interval tended to increase with increasing age and to decrease with increasing heart rate. We believe that instead of setting one definite figure for the upper limit of normal for children's electrocardiograms it would be a better plan, if sufficient data were available, to secure a statistically significant average for each age and heart rate and to construct a table giving the upper limits of the P-R at the various ages and heart rates. If a more reliable approximation of the size of the heart were available (perhaps the surface area, as suggested by Kissane), this could be used in the table instead of the age.

The average duration of the QRS group was 0.065 second. The QRS showed an increase in duration with the increase in age. We agree with other authors in placing the upper limit for duration of the QRS for children at 0.09 second, or at less for young children and infants. QRS of low voltage was found in only 1 of 100 electrocardiograms of normal children. There is no great difference between the heights of the R-wave for children and those for the R-wave of adults. We found the average to be slightly higher for children. Other authors have found it much higher and others lower.

Slight slurring of the deflections of the QRS may be found, frequently of the R-wave in Lead II, but definite or conspicuous slurring is almost never found in an electrocardiogram of a normal child.

The electrical axis in all but 3 cases lay between 20 and 104 degrees, ranging from a slight left axis deviation to a slight right axis deviation.

Slight shifting of the RS-T segment, especially upward, is occasionally seen in a normal child's electrocardiogram.

The T-waves consistently averaged higher for the boys than for the girls, even when the data were separated according to the various age groups. We have no explanation of this difference. It will be seen in Part II that this difference according to sex is also found in the electrocardiograms of children with heart disease.

T_3 frequently inverted or diphasic in the electrocardiogram of the normal child.

Low T-waves were found in only 1 case, and the normality of this picture should be doubted, since T_2 was slightly diphasic. No notched T-waves were found.

Like many previous investigators, we found the Q-T to vary with the heart rate, but we found no difference according to sex, such as is found in the electrocardiograms of adults.

Premature beats are rare in children with normal hearts.

AUTHOR.

Drawe, Catherine E., Hafkesbring, Eleanor M., and Ashman, Richard: II. The Changes in Children's Electrocardiograms Produced by Rheumatic and Congenital Heart Disease. Am. J. Dis. Child. **53**: 1470, 1937.

The electrocardiograms of 100 children with rheumatic heart disease and of 50 children with congenital heart defect were carefully measured (the heights of the individual deflections and the various intervals of the cardiac cycle), and the averages for the different intervals were compared with those found in the electrocardiograms of the normal group (Part I).

The Rheumatic Group.—The principal abnormalities of the P-wave in the electrocardiograms of children with rheumatic heart disease are definite and conspicuous notching, widening, and slight increase in height.

The P-R interval is definitely prolonged in a large percentage of cases of rheumatic heart disease.

The abnormalities of the QRS complex are relatively slight, consisting of a small increase in duration and occasional notching or slurring of the individual waves.

Only a slight tendency to right axis deviation was shown in the electrocardiograms of children with mitral stenosis and insufficiency. This was probably due to the fact that in most of our cases the condition was not far advanced. The children with aortic regurgitation showed a definite tendency to left axis deviation.

The incidence of shifts of the RS-T segment is increased, but not so markedly as had been reported elsewhere. However, we were unable to follow our patients closely and to make additional electrocardiograms during the course of the rheumatic fever.

Abnormalities of the T-waves were found in 10 per cent of the cases. These abnormalities consisted of low T-waves in all leads (below 1 mm.), diphasic T-waves in Lead I, and low, rounded, notched, and inverted T-waves in Lead II.

The Q-T interval is often definitely prolonged in cases of rheumatic heart disease.

As with the normal children, the incidence of premature beats is low.

Not all children with rheumatic heart disease have abnormal electrocardiograms.

Even though the electrocardiogram of a child is not definitely abnormal the presence of any one of the aforementioned abnormalities should suggest the possibility of rheumatic heart disease.

The Group With Congenital Defect.—The outstanding abnormalities of the P-wave were an increase in the width and in the height, and these were found chiefly in the electrocardiograms of children with pulmonary stenosis and tetralogy of Fallot and to a lesser degree in those of children with interventricular septal defect. The notching of the P-wave was not beyond normal limits.

The P-R interval was approximately the same as it was in the electrocardiograms of the normal group, but it may be considered to have been slightly prolonged

on the average, since the children's mean age was a few years younger in the group with congenital heart defect than in the normal group.

The average duration of the QRS in the electrocardiograms of children with congenital heart defect was longer than that in the electrocardiograms of normal children, even though the children were younger. This increase in duration was due mainly to the influence of the children with pulmonary stenosis.

Notching and slurring of the QRS occurred frequently in the electrocardiograms of children with pulmonary stenosis, occasionally in those of children with interventricular septal defect and rarely in those of children with patent ductus arteriosus.

All the electrocardiograms of children with pulmonary stenosis showed extreme, conspicuous or definite right axis deviation, ranging from 99 to 179 degrees, and in 1 case, not included when the average was computed, the deviation was 125 degrees.

The T-waves averaged considerably higher than those in the electrocardiograms of the normal group. As with the normal children, the boys' T-waves averaged higher than those of the girls.

Abnormalities of the T-waves are occasionally found, consisting of inversions of T_2 and deep inversions of T_3.

The Q-T interval was slightly prolonged in a few instances.

AUTHOR.

Gross, Louis, and Silverman, Gertrude: The Aortic Commissural Lesion in Rheumatic Fever. Am. J. Path. **13**: 389, 1937.

There has been described in this report the findings in 70 cases of rheumatic fever segregated into six groups according to the clinical course taken by the disease. It is shown that a number of inflammatory changes are found in the aortic root, wedge, annulus, ring, subaortic angle, and pericardial mantle which are characteristic of rheumatic fever and, to some extent, reflect the clinical course of the disease. Even when healing takes place the histological characteristics of the commissural lesion afford additional stigmata which are of value in discerning a past rheumatic process. A discussion is given of the pathogenesis of this lesion from which it appears that even though the original infection may reach the aortic ring through several routes, in most instances the inflammatory granulation tissue passes from the pericardial mantle through the aortic root, wedge, and annulus to reach the aortic rings. The latter show a much more flagrant inflammatory process which spreads into the valve leaflets and, probably with the additional factor of trauma caused by the systolic and diastolic movements of the cusps, eventually leads to their agglutination. The possible significance of these findings in relation to the pathogenesis of the so-called congenital bicuspid aortic valve is indicated. A description is also given of the histological and topographical changes taking place during the different age periods in the normal aortic commissural region.

AUTHOR.

Hess, L.: Pathology of Syphilitic Aortitis. Klin. Wchnschr. **15**: 898, 1936.

In this presentation the author shows that 62 per cent of the cases of syphilitic aortitis had a heredity of vascular disability, which is much higher than in a control series. He considers this of significance in the occurrence of vascular involvement in syphilis.

L. N. K.

Porter, R. E., and Gordon, Wm. H.: The Size of the Heart in Pulmonary Tuberculosis. Am. Rev. Tuberc. **36**: 82, 1937.

A study was made of the teleoroentgenograms of 400 patients having pulmonary tuberculosis.

Their ages ranged from eighteen to sixty-seven years.

The study included all clinical types of pulmonary tuberculosis.

A comparison was made between the measured transverse diameter of the heart and the predicted transverse diameter.

Of the 400 patients, 203 (50.5 per cent) had a measured transverse diameter greater than the predicted diameter, 165 (41.5 per cent) had a measured transverse diameter of less than the predicted diameter and 32 (8 per cent) had a measured transverse diameter equal to the predicted diameter.

As is shown in Table 2, in a study of the x-ray films of the 54 patients that died, there was very little difference noticed as compared with the general average.

AUTHOR.

Leubner, H.: Rare Cancers of Blood Vessel Endothelium. Frankfurt. Ztschr. f. Path. **49**: 63, 1936.

A case of hemangioendotheliomatosis of the liver, spleen, and skin in a twenty-six-year-old man is described which is interpreted as a primary multiple cancerous growth. A second case of diffuse lymphangioendothelioma in an eighteen-year-old boy is reported. This caused elephantiasis of the genitalia, abdominal wall, and both extremities. This was also found to be cancerous on histological examination.

L. N. K.

Radasch, H. E.: Glomal Tumors. Arch. Path. **23**: 615, 1937.

Ninety glomal tumors have been reported to date. They have a wide anatomical distribution. Once classed as angiomata, they are now known to result from hyperplasia of an arteriovenous anastomosis (digital glomus). The normal glomus is a distinct structural unit or organ consisting of an afferent arteriole, a Sucquet-Hoyer canal, a primary collecting vein, intraglomar reticulum, and a capsular portion.

The article deals largely with anatomical and pathological structure, but quotes articles in which physiological deductions are made. For instance, the normal glomus may play an important part in the regulations of peripheral blood flow, of blood pressure, and of temperature regulation by heat loss.

Glomal tumor is typically attended by exquisite tenderness over the tumor and by considerable pain over a wide area surrounding the tumor. Excision is the only treatment, and is universally effective.

H. M.

Beneke, R.: Intimal Fibrosis (Endarteriitis obliterans) as a Sequel to Local Flow Anomalies. Ztschr. f. Kreislaufforsch. **29**: 146, 1937.

The argument is presented that intimal fibrosis results from abnormalities in flow at the site of fibrosis.

L. N. K.

Baker, A. B.: Structure of the Small Cerebral Arteries and Their Changes With Age. Am. J. Path. **13**: 453, 1937.

This investigation was made because there are few reports on the structure of normal cerebral vessels. Quoting from the "Conclusions": The average small cerebral artery differs in structure from similar sized vessels elsewhere in the body in that it contains within its media a relative paucity of both elastic and

muscle tissue and a predominance of collagenous fibers. The very small cerebral arteries are composed almost strictly of collagenous tissue and may appear as a cerebral fibrosis. With the advance of age the elastica interna of the cerebral arteries becomes reduplicated and frequently loses its normal tinctorial properties. The media undergoes a rapid fibrosis. It frequently shows a hyalinization and more rarely a calcification of all of its elements.

H. M.

Schretzenmayr, A.: The Rôle of the Medium and Large Arteries in Regulating the Circulation. Klin. Wchnschr. **15:** 625, 670, 1936.

The author's studies with arterial oncometry show that the medium and large vessels play an important rôle in regulating the circulation. (This is not convincing.) These studies also show that sclerosis of the large vessels noticeably alters the work of the heart.

L. N. K.

Gebert, W.: Capillary Function and Menstruation. Klin. Wchnschr. **15:** 828, 1936.

The latent period in developing dermographia was determined at various times in the menstrual cycle. Preceding menstruation, the latent period at first decreases and then increases until menstruation begins, after which it decreases rapidly to normal.

L. N. K.

Roboz, P.: Capillary Function Tests. Klin. Wchnschr. **15:** 968, 1936.

The velocity of skin capillary flow is determined under the microscope (1) at room temperature and (2) after immersion in water at a temperature of 50° C. for ten minutes. The usual effect of heat is to make the flow so rapid that the movement of the red blood cells cannot be measured. In certain instances, however, the heat causes stasis.

L. N. K.

De Takats, Geza, Hick, Ford K., and Coulter, John S.: Intermittent Venous Hyperemia in the Treatment of Peripheral Vascular Disease. J. A. M. A. **108:** 1951, 1937.

The authors present a method of comparing the peripheral vascular effects of intermittent venous hyperemia and of intermittent suction and pressure by means of oscillometer curves and venous oxygen determinations. They state that "the paucity of data does not permit conclusions;" also that "certain variable factors make comparable controls very difficult."

H. M.

Schneyer, K.: Observations on the Peripheral Circulation by Experimental Aortic Insufficiency. Arch. f. exper. Path. u. Pharmakol. **181:** 481, 1936.

Microscopic examination of the rabbit's mesentery showed a vasoconstriction following production of aortic insufficiency by valve destruction. This vasoconstriction does not occur when the four blood pressure regulator nerves (the carotid sinus and aortic nerves) are sectioned. No capillary pulse was observed in the rabbit following production of aortic insufficiency but exaggeration of the pulsatory movement in the larger arteries was noted in the microscopic field.

L. N. K.

Wezler, K., and Standl, R.: The Normal Age Curve of Pulse Wave Velocity in Elastic and Muscular Arteries of Man. Ztschr. f. Biol. **97**: 265, 1936.

The curves of the pulse wave velocities for the aorta and of the arteries of the arm and leg at various ages are given. These are related to the changes in elasticity of these vessels. The earlier age at which acceleration of the pulse wave velocity occurs in the leg as compared to that in the arm indicates earlier sclerosis of the vessels in the leg.

L. N. K.

Gross, D.: The Clinicostatic Respiratory Signs in Decompensated Cardiac Patients. Ztschr. f. Kreislaufforsch. **29**: 113, 1937.

The influence of the recumbent position on vital capacity and breath holding was determined in twenty individuals without heart disease and twenty with cardiac disease and various degrees of congestive heart failure. These values were determined in the reclining and sitting positions. In well persons little or no change on vital capacity or breath holding was found. In cardiac patients a noticeable reduction of vital capacity and breath holding was found. This is used as a clinicostatic index of heart function. (An examination of tables shows that the effect of posture, by and large, is proportional to the reduction below normal of the vital capacity and breath holding.)

L. N. K.

Lucas, M.: Air Emboli in Coronary Arteries Following Artificial Pneumothorax in a Thirty-Year-Old Patient. Beitr. z. Klin. d. Tuberk. **88**: 223, 1936.

In refilling an old left-sided pneumothorax a pulmonary vein was entered and a fatal air embolism resulted. In addition to air emboli in the cerebral vessels a massive air embolus of the left coronary artery was demonstrated postmortem. There were hemorrhagic areas of necrosis in the wall of the left ventricle. Death in this case was preceded by tachycardia and unconsciousness.

L. N. K.

Radnai, P., and Mosonyi, L.: Venous Air Emboli. Ztschr. f. d. ges. exper. Med. **98**: 755, 1936.

In acute air embolism of venous origin air can be demonstrated in the left side of the animal's heart both by roentgen ray and postmortem. The results of air injection as far as death is concerned are not predictable. Electrocardiographic changes are found indicating disturbances in coronary circulation. These are reversible in animals that survive.

L. N. K.

Blalock, Alfred, Robinson, C. S., Cunningham, R. S., and Gray, Mary E.: Experimental Studies on Lymphatic Blockage. Arch. Surg. **34**: 1049, 1937.

Complete blockage of the lymphatic system has never been produced experimentally. The explanation of this fact must lie in the capacity for the development of a collateral circulation. Experiments have been performed on 52 dogs and 22 cats in which an attempt was made to produce a complete blockage of the lymphatics by various procedures which included ligation and the injection of sclerosing agents into the lymphatics. In three of the animals, complete lymphatic blockage was produced. This resulted in an almost complete disappearance of the lymphocytes and eosinophiles from the blood stream. The animals lost weight and were killed when it became apparent that they were going to die. Examination at autopsy revealed

the lymphatics of the abdominal organs to be markedly distended and there was extravasation of chyle into many of the tissues. No lymphaticovenous communications could be determined. In the other animals, the lymphatic obstruction was temporary. In these animals, a similar but temporary change was noted in the blood picture.

E. A. H.

Lazarovits, L.: Aortic Pain and X-ray Irradiation. Wien. klin. Wchnschr. 49: 755, 1936.

The author used x-ray irradiation in 27 cases of pain due to syphilitic aortitis. He used 50 per cent of the erythema dose and radiated both from the front and back; as many as 10 treatments were used. In 11 of these patients a lasting and definite relief of pain was found. Patients having angina pectoris were not relieved.

L. N. K.

Gold, Harry, Kwit, Nathaniel T., and Otto, Harold: The Xanthines (Theobromine and Aminophylline) in the Treatment of Cardiac Pain. J. A. M. A. 108: 2173, 1937.

The effect of theobromine and aminophylline on cardiac pain was studied in a group of 100 ambulant patients with angina pectoris.

These patients were selected on the basis of proof of organic heart disease, cardiac pain on effort, little or no physical work, and faithful cooperation.

An attempt to include only patients who could distinguish relief afforded by glyceryl trinitrate from relief by a soluble placebo tablet taken in the same way during an attack of pain was abandoned, because a fairly large number of patients with cardiac pain were found who could not distinguish between the two. This is due to the transient character of effort pain in a large proportion of the patients.

The effect studied was the influence on the severity and frequency of attacks and on the capacity for effort without pain, not relief during attacks of pain.

The data consisted of the patients' judgments regarding changes in pain. These data were secured in a manner relatively free of bias by the use of the "blind test."

In all, 209 courses of treatment with the xanthines were given, each course being alternated with a course in which a placebo (or some other agent) was used.

The doses of the xanthines were from 15 to 60 grains daily of theobromine, and from 9 to 12 grains daily of aminophylline.

Changes in the amount of pain were charted. Cause and effect were established by a method relatively free of personal judgments; namely, by comparing sections of the chart representing periods in which a placebo of lactose (or some other agent) was taken with those in which a xanthine was administered.

The xanthines were without appreciable influence on the blood pressure.

Every type of change in pain observed during the use of a xanthine was reproduced in the same individual by a period in which a placebo was used.

The results show, therefore, that patients with cardiac pain are unable to distinguish the effects of a placebo from those of a xanthine when measures are taken to preclude the identification of the agent by any means other than the relief of pain. It is concluded that the xanthines exert no specific action which is useful in the routine treatment of cardiac pain.

AUTHOR.

Bernhardt, H.: Effect of Cortical Hormone and Vitamin C on Circulatory Collapse of Diphtheritic Origin. Deutsche med. Wchnschr. 62: 1123, 1936.

The author has used, in malignant diphtheria, intravenous injections of 10 c.c. of an adrenal cortical hormone, 2 c.c. of Vitamin C preparation, 20 c.c. of 10 per cent

glucose and 5 to 10 c.c. of NaCl. He found the results very satisfactory and obtained relief of the symptoms of circulatory collapse. The procedure should be used immediately when signs appear. Small repeated doses are better than a single large one. This medication works better than camphor, cardiazol, or coramin. Digitalis is counterindicated in the condition.

L. N. K.

Külbs, F.: The Clinical Significance of Heart Enlargement. Med. Klin. 32: 522, 1936.

Regulation of patients' activities and small doses of digitalis permit long life in patients with auricular fibrillation and large hearts. When congestive failure is present, intensive medication with digitalis and strophanthus is indicated.

L. N. K.

Kisch, F.: Therapy in and Criteria for Judging Effect in Intermittent Claudication. Wien klin. Wchnschr. 49: 712, 1936.

The author used an exercise test to determine efficacy of treatment. This consisted in determining the number of flexions of the limb at the knee which cause pain when the patient is lying flat in bed. Both nitroglycerine and euphyllin cause an increase in the exercise tolerance in patients with intermittent claudication; in some instances, in fact, pain could not be elicited after therapy. The author has used prolonged medication with nitroglycerine and euphyllin—the former under the tongue, and the latter intravenously or as a suppository—in ten patients with intermittent claudication. Marked improvement was observed in five of these patients in the course of a year, the improvement was slight in two others and absent in the remaining three.

L. N. K.

Weiss, Soma: Vagal Reflex Irritability and the Treatment of Paroxysmal Auricular Tachycardia With Ipecac. Am. J. M. Sc. 194: 53, 1937.

Ipecac is a useful agent in the treatment of paroxysmal auricular tachycardia.

In 11 cases attacks were relieved following the oral administration of doses of from 4 to 32 c.c. (1 to 8 drams) of syrup of ipecac.

The pharmacologic principle underlying this method of treatment and the considerations to be observed in its application are described.

The relation of the physiologic state of the autonomic nervous system, and particularly of the sensory-vagal reflexes, to the effective treatment of paroxysmal auricular tachycardia is discussed. The more powerful the vagal stimulus applied and the more increased the tonus of the specific reflex, the greater is the probability of therapeutic success.

The pronounced variations in the tonus and in the irritability of the various cardiac inhibitory reflexes are the basic causes underlying the variability of effectiveness of measures used in the treatment of paroxysmal auricular tachycardia.

AUTHOR.